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OF
THE JOHNS HOPKINS HOSPITAL

(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

(SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY)

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NUMBER 1

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THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL
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July, 1946

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THE EFFECT OF PENICILLIN IN EXPERIMENTAL INTESTINAL OBSTRUCTION

Studies on Strangulated Low Ileal Obstructions

ALEXANDER BLAIN III, M.D.,[1] AND JOHN D. KENNEDY, M.D.[2]

From the Departments of Surgery and Pathology of the Johns Hopkins Medical School and the Johns Hopkins Hospital

Recent advances in electrolyte and water replacement therapy and in methods of decompressing distended obstructed bowel have, together with improved surgical techniques, so lowered the mortality in intestinal obstruction that the old theory of the existence of a "toxemia" in this condition has all but been abandoned by many surgeons. The present mortality is still too high, and further study of the possible role of toxemia is indicated. It has recently been demonstrated that, in dogs with isolated obstructed jejunal loops, death is due to the action of bacteria or their products, and furthermore that these animals can be protected for a significant period of time with large doses of penicillin (Harper and Blain (1)). Sulfasuccidine, likewise gives protection in dogs with isolated jejunal loops (Poth and Firor (2), Harper and Blain (3)). It has been demonstrated that sulfasuccidine also affords protection in experimental lesions in which the mesenteric blood supply to the ileum is impaired but in which the bowel lumen is not obstructed (Sarnoff and Poth (4), Sarnoff and Fine (5)). While the experiments cited have been of value in determining the importance of the role of bacteria in intestinal obstruction they have not been directly applicable to the problem of the management of intestinal obstruction in man because 1) the closed isolated loop preparation has no exact clinical counterpart, and 2) the sulfasuccidine experiments have indicated that this drug must be given for several days before effective bacterial depopulation of the

[1]William Stewart Halsted Fellow in Surgery and Assistant in Pathology.
[2]National University of Ireland Fellow in Pathology.

The bacteriological studies were performed by Jerome Rosenfeld of the Department of Bacteriology, the Graduate School, Johns Hopkins University and by James W. Johnson of the Biological Division of the Medical Clinic, Johns Hopkins Hospital.

intestine is accomplished, and therefore is not so effective when administered after strangulation of the bowel has occurred.

In an attempt to correlate the promising results of the above mentioned experiments with the problem of intestinal obstruction in man, as it exists today, two studies have been carried out. The first consisted of a survey of all the acute cases of complete small bowel obstruction operated on in this hospital during the past ten years. These cases were studied with particular reference to the need for anti-bacterial therapy should such therapy prove successful in similar lesions in dogs. In this study (Calihan, Kennedy and Blain (6)) it was shown that bacteria play an important part in maintaining the present mortality rate due to intestinal obstruction at around twenty per cent. This role is, of course, most important in strangulated obstructions and in the total series studied twenty seven per cent showed marked discoloration of the bowel, or gangrene at operation.

The second study, the results of which are to be reported in this paper, was designed to determine the importance of the role played by bacteria or bacterial products in simple strangulated low ileal obstructions in dogs. To accomplish this two groups of dogs having this type of obstruction were treated for hemorrhage, shock, dehydration and electrolyte loss. One group was treated in addition, with massive doses of penicillin. The other group was not treated with penicillin and these dogs served as controls.

EXPERIMENTAL METHODS

Simple strangulated obstructions of the low ileum were created in all dogs reported in this paper in the following manner. The terminal ileum was delivered through a right rectus incision and was transected between clamps at a point just proximal to the termination of the anti-mesenteric artery of the ileum. The proximal and distal ends were turned in by the closed technique of Parker and Kerr. The distal segment was anchored to the anterior parietal peritoneum to prevent intussusception. The veins to a sixty centimeter segment of the ileum proximal to the point of transection were then ligated with double silk ties (Fig. 1). Both arteries and veins running parallel to the bowel towards the selected segment were tied off and the mesentery at either end of the segment was divided down to its base. The blood

FIG. 1. METHOD OF TYING OFF MESENTERIC VEINS TO ILEAL SEGMENT.
Note intact blood supply to proximal turned in end. a. Proximal turned in end. b. Distal turned in end. c. Rent in mesentery at distal extremity of segment to be strangulated. The vessels running parallel to the bowel towards the segment to be strangulated are occluded at rent in mesentery.

supply to the proximal turned in end was left intact and the lower limit of the segment to be strangulated was several centimeters above the turned in end. In all cases the strangulated segment of ileum measured sixty centimeters at the beginning of the procedure and at least fifty centimeters at the end of the procedure. If the affected bowel had so contracted that it no longer measured fifty centimeters more bowel was strangulated by tying off additional veins. In all cases the affected bowel was cold and black or deep purple and had begun to exude sanguinous fluid when returned to the abdomen. On later post-mortem examination the affected segment was always found to be black or dark purple, heavy and edematous, and distended and stretched so that it measured at least seventy centimeters in length, and its walls showed varying degrees of necrosis.

All animals were operated on under intravenous nembutal anesthesia. Picrotoxin was used when necessary for respiratory depression. Food was withheld for twenty-four hours preoperatively and food and oral fluids were withheld for the duration of the animals' survival except in two dogs treated with penicillin which subsequently underwent successful resection and anastomosis. The operating time averaged about forty-five minutes for all animals.

Immediately following operation all dogs were given five hundred cc. of whole blood via a femoral vein cut-down and also five hundred cc. of normal saline solution subcutaneously. Blood was taken preoperatively for a hematocrit reading. This was repeated usually every two to four hours postoperatively throughout the first forty hours and at greater intervals thereafter in the case of the dogs surviving this long. A drop of five degrees in the hematocrit reading was considered evidence of the need for additional whole blood while a rise in hematocrit was considered evidence of the need for additional saline. If the hematocrit continued to rise in spite of more saline solution, seven per cent gelatin solution was administered intravenously. A few direct measurements of the systolic blood pressure were made in some of the dogs.

As has been mentioned one group of dogs (ten) were not treated with penicillin and served as controls. The other group of ten dogs were treated with massive doses of penicillin administered intramuscularly. The dosage for these latter animals was as follows:

100,000 units every two hours during twenty four hours beginning from between one half hour to three hours postoperatively, 50,000 units every two hours during the next forty eight hours and 50,000 units every four hours during the remainder of their survival. In the case of two dogs which underwent resection at seventy-two hours 50,000 units of penicillin every two hours were administered during the twenty-four hours following this operation. Thus the total dosage for the treated dogs in the first twenty four hours after the beginning of treatment was 1,200,000 units and by the end of the first seventy hours, 2,400,000 units. One dog that lived a hundred hours received by the above schedule, a total of 2,750,000 units of penicillin. Penicillin levels were determined in two dogs (#101 and 102) using a modification of the method of Rammelkamp (7). These levels were respectively 3.8 and 1.4 units per cc. of serum.

Cultures of the intestinal contents at the site of operation were made in all dogs to be treated with penicillin. Five cubic centimeters of sterile saline which were introduced into the distal segment of transected bowel via a needle through a purse string suture, were withdrawn and placed in a culture tube. At autopsy, which was performed immediately following death, cultures were made of the intestinal tract above the site of the obstruction, of the bloody peritoneal transudate and the heart blood in all cases. In addition, at autopsy the strangulated obstructed segment was removed, measured, photographed and then placed in formalin along with sections of the major organs. Microscopic sections of tissues removed at autopsy were made and bacterial stains were done on all sections of the intestine.

Blood specimens were taken from all dogs just before or immediately after death for chloride and hematocrit determinations. In addition, in seven dogs other determinations such as the non protein nitrogen, total serum protein, calcium, phosphorus, sodium, potassium and carbon dioxide combining power were made. In eight dogs temperatures were taken and charted.

RESULTS

I. Control Dogs

The survival time for these animals ranged between sixteen and thirty five hours (Chart I). The hematocrit determinations and the

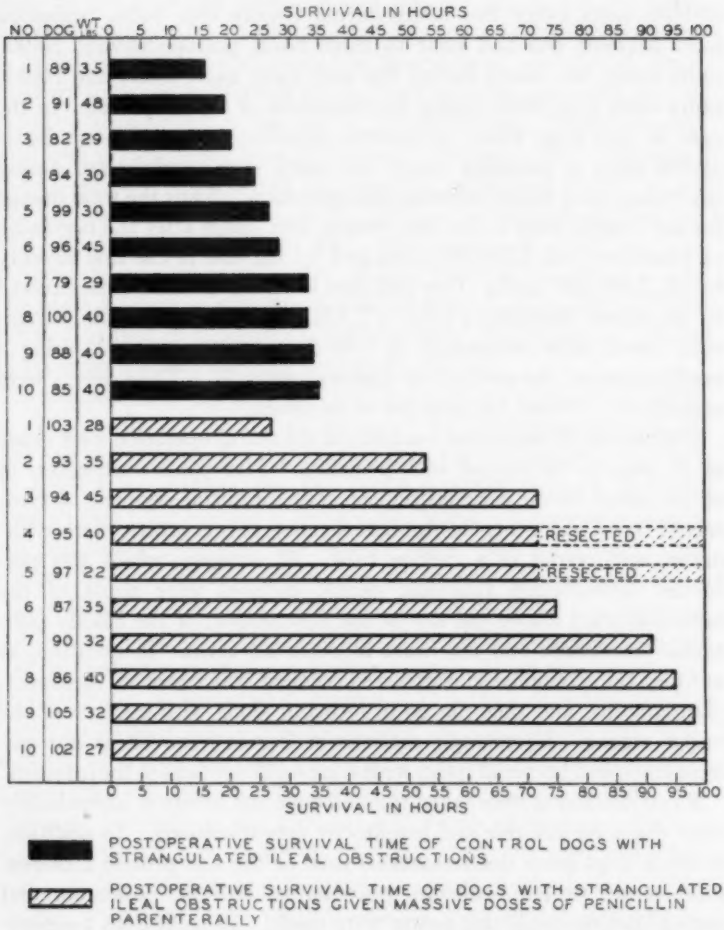
SURVIVAL IN HOURS
NO DOG WT
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
1 89 35
2 91 48
3 82 29
4 84 30
5 99 30
6 96 45
7 79 29
8 100 40
9 88 40
10 85 40
1 103 28
2 93 35
3 94 45
4 95 40 RESECTED
5 97 22 RESECTED
6 87 35
7 90 32
8 86 40
9 105 32
10 102 27
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
SURVIVAL IN HOURS
POSTOPERATIVE SURVIVAL TIME OF CONTROL DOGS WITH STRANGULATED ILEAL OBSTRUCTIONS
POSTOPERATIVE SURVIVAL TIME OF DOGS WITH STRANGULATED ILEAL OBSTRUCTIONS GIVEN MASSIVE DOSES OF PENICILLIN PARENTERALLY

Chart 1. Diagram Showing Relative Survival Times of Dogs with Strangulated Ileal Obstructions Not Treated with Penicillin as Constrasted with the Survival Times of Dogs with Strangulated Ileal Obstructions Treated with Penicillin

Both groups were treated for hemorrhage, shock, chloride and water loss

fluids administered to combat hemorrhage and shock are plotted for each dog in Table 1. The symptomatology was the same for all dogs. They would be awake and standing in their cages in from two to ten hours postoperatively. Within four to sixteen or twenty hours postoperatively, the dogs would vomit foul smelling bloody material which was red if vomited early and dark reddish brown later. There was a good deal of variation in the severity and amount of vomiting. More subcutaneous saline was given to the dogs which vomited excessively than to those which did not. Ascites which was always bloody at autopsy became clinically evident within five hours after operation. Often large distended loops of bowel were both palpable and visible beneath the wall of the abdomen. The manner in which the dogs died was remarkable. In some cases they would appear to be in relatively good condition and in the process of standing or walking would literally suddenly gasp and drop dead. In others there was a terminal "toxic" stage of rather sudden onset which might last as long as thirty minutes or an hour. This stage was characterized by excessive retching and vomiting followed by rapid respirations, a rapid thready pulse and coma. Animals dying in this manner would always stand with head down during the retching and vomiting, then they would lie or fall down during the terminal coma. If attempts were made to stand the animal on its feet after it had fallen or lain down it was found that all four limbs were paralyzed and would buckle beneath it. Death was heralded in all animals by rigidity and extension of the limbs. In three of five control dogs in which the alterations in rectal temperature were followed there was a terminal elevation to 105°. In the other two dogs no terminal elevation was noted. In general it can be said that clinically the manner of death in these animals did not resemble the manner of death in dogs with shock. Dogs dying in shock are very weak for a long time before death and seem to die slowly rather than to topple over dead or fall in sudden coma. This type of death was observed in controls in which there was no gross perforation, and indeed also in the dogs treated with penicillin. Three dogs intended for controls bled steadily after operation. The hematocrit fell steadily and there was poor postoperative response in spite of intensive blood replacement therapy. These dogs are not included in this report. A fourth dog in which there was strangulation of the turned in end with

leakage of bowel contents into the peritoneal cavity was also excluded from the control series.

At autopsy all strangulated ileal segments measured between seventy and one hundred centimeters in length. These segments were swollen and thick, moist and black or dark purple (Fig. 2). The bowel above the obstruction was distended except where there had been a gross perforation in which case it was collapsed. The lumen of the obstructed bowel was filled with dark, foul smelling blood which was sometimes partly clotted. The peritoneal cavities contained between five hundred and two thousand cubic centimeters of bloody transudate having the composition of blood serum and a hematocrit of around fifteen. All strangulated segments showed gross and microscopic evidence of ulceration, necrosis of the intestinal wall and marked hemorrhage into the wall. There was always a marked ulcerative diphtheritic enteritis and also infection of the damaged and necrotic intestinal wall. In some cases, especially in those in which gross perforation had occurred, necrosis of the wall was so marked that no viable tissue remained. This was more characteristic of the antimesenteric border than of the mesenteric border. Bacterial stains revealed the presence of many types of bacteria, both Gram positive and Gram negative.

II. Dogs Treated with Massive Doses of Penicillin

Of the ten dogs treated with massive doses of penicillin one died twenty six hours after the operation. Nine dogs were protected for fifty hours or more and eight dogs (eighty per cent) for seventy two hours or more. Four dogs (forty per cent) survived ninety hours or longer and one dog lived for a hundred hours (Chart I). Two dogs at seventy two hours (a period twice as long as any control survived) underwent successful resection of their strangulated obstructions and side-to-side anastomosis. These two dogs survived for over a month at which time one was sacrificed.

Following strangulation these dogs behaved essentially as the control dogs. In these dogs with a longer survival time the vomitus eventually became non-bloody. When they died most did so in a manner similar to that described for the control dogs. In the dogs surviving over ninety hours death was preceded by a more prolonged

(two to three hours) "toxic" stage. In these animals this stage was characterized by severe retching and vomiting sometimes associated with carpal-pedal spasm. Before death the fore-limbs and hind-limbs became completely paralyzed so that the animal could not stand. The respiration became fast and the pulse rapid and thready. The one treated dog which died in twenty seven hours never responded well after operation but its hematocrit at death was not low and no abnormalities other than the strangulated obstruction could be found at autopsy.

Only one dog treated with penicillin (#90) showed at autopsy a gross perforation of the strangulated ileal obstruction. The strangulated bowel in the other nine dogs (Figs. 3, 4, 5) resembled that of the control dogs in which there was no perforation. In general, then, the strangulated bowel in nine of the ten treated dogs was thick and firm, whereas in five of the ten control dogs there were large areas of friable, tissue paper thin and perforated bowel wall. Otherwise the gross findings at autopsy did not differ from those described for the control dogs. The microscopic sections of the strangulated segments of the penicillin treated dogs also showed hemorrhage, necrosis and ulceration and both Gram positive and Gram negative organisms. However, the amount of infection was definitely less. The degree of ulceration and necrosis was sometimes less marked in treated dogs dying early. In some of the dogs surviving over seventy hours submuscosal healing in the form of fibrosis and scarring was beginning to occur.

The hematocrit determinations and fluids given to combat hemorrhage and shock in the dogs treated with massive doses of penicillin are plotted in Table 2. Four dogs intended for the series of treated dogs were excluded for the following reasons: Strangulation of the proximal turned in end with leakage of bowel contents into the peritoneal cavity (2 dogs) massive necrosis of the liver (2 dogs, including one just mentioned) and aspiration pneumonia with pulmonary edema (1 dog).

III. Blood Chemical Studies

It was necessary to obtain terminal chloride values in order to judge the efficacy of our parenteral physiological saline therapy, and to eliminate the factor of hypochloremia from our experiment. In all

TABLE 1

Control Dogs. Hematocrits and Fluid Therapy.

DOG	HEMATOCRIT AND FLUIDS	HOURS POSTOPERATIVE																						TOTAL FLUID
		0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	45	50	55	
79	Hematocrit	46		50		44								34			45	47								1000 cc. blood
(29 lb.)	cc. blood i.v.		500											500												1000 cc. gelatin
	cc. gelatin i.v.			500				500																		1300 cc. saline
	cc. saline s.q.		500					300						500												in 33 hr.
82	Hematocrit	35		46	48		53		48	40		39														1000 cc. blood
(29 lb.)	cc. blood i.v.		500			500																				500 cc. gelatin
	cc. gelatin i.v.							500																		1000 cc. saline
	cc. saline s.q.		500					500																		in 20 hr.
84	Hematocrit	39			31	27			33				30													1100 cc. blood
(30 lb.)	cc. blood i.v.		500			300																				500 cc. gelatin
	cc. gelatin i.v.				500																					800 cc. saline
	cc. saline s.q.		500						300																	in 24 hr.
85	Hematocrit	39		36		35					30					37		35								1030 cc. blood
(40 lb.)	cc. blood i.v.		500					250						300												500 cc. gelatin
	cc. gelatin i.v.				500									300	(plasma)											300 cc. plasma
	cc. saline s.q.		500					250																		750 cc. saline
																										in 35 hr.
88	Hematocrit	52		50		44		38		33			34		31			30								1700 cc. blood
(40 lb.)	cc. blood i.v.		500				400			500							300									
	cc. gelatin i.v.																									1500 cc. saline
	cc. saline s.q.		500		200					500							300									in 34 hr.
89	Hematocrit	41		37	30			27	28																	1300 cc. blood
(35 lb.)	cc. blood i.v.		400				400	500																		500 cc. gelatin
	cc. gelatin i.v.			500																						900 cc. saline
	cc. saline s.q.		500			400																				in 16 hr.
91	Hematocrit	45		45	38		39	36		32																1200 cc. blood
(48 lb.)	cc. blood i.v.		500	300		400																				500 cc. gelatin
	cc. gelatin i.v.							500																		500 cc. saline
	cc. saline s.q.		500																							in 19 hr.
96	Hematocrit	47		48		43	49					41		41		41										1250 cc. blood
(45 lb.)	cc. blood i.v.		500			500		250																		1800 cc. saline
	cc. gelatin i.v.													500												in 28 hr.
	cc. saline s.q.		500			500		300						500												
99	Hematocrit	42	50		40	43	45	40			27		35	37	35											1200 cc. blood
(30 lb.)	cc. blood i.v.		500			500							200													250 cc. plasma
	cc. gelatin i.v.				250	(plasma)																				2000 cc. saline
	cc. saline s.q.		500			500			500	500																in 26.5 hr.
100	Hematocrit	42		49		46		43					35	37			37	39								1300 cc. blood
(40 lb.)	cc. blood i.v.		500			300								500												1800 cc. saline
	cc. gelatin i.v.																									in 33 hr.
	cc. saline s.q.		500			300		600							300											

TABLE 2

Dogs Treated With Penicillin. Hematocrit and Fluid Therapy.

(40 lb.)	cc. blood i.v.			500																											1800 cc. saline
	cc. gelatin i.v.																														in 33 hr.
	cc. saline s.q.			500				300				600								300											

TABLE 2

Dogs Treated With Penicillin. Hematocrit and Fluid Therapy.

DOG	HEMATOCRIT AND FLUIDS	HOURS POSTOPERATIVE																												TOTAL FLUID
		0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	45	50	55	60	70	80	90	100	
86	Hematocrit	47	52	57	32	32	29	33	35				38	16	20		27		28			28	27		24	22	21	39	53			2300 cc. blood
(40 lb.)	cc. blood i.v.		500					500								500										300		500			1000 cc. gelatin
	cc. gelatin i.v.						500						500																		3600 cc. saline
	cc. saline s.q.		500					500					500							300			300		300		300	300	600		in 95 hr.
87	Hematocrit	48		50	30	36	36	36	37			33	20		21	22			26		26		29	30		30	33				1400 cc. blood
(35 lb.)	cc. blood i.v.		500			400									500																1000 cc. gelatin
	cc. gelatin i.v.			500								500																				2000 cc. saline
	cc. saline s.q.			100		500						500								300					300	300						in 95 hr.
90	Hematocrit	33			37			40	35			27		25			27		29		30		32	33	31	36	27	29	28		1600 cc. blood
(32 lb.)	cc. blood i.v.		500			500									300					300											1000 cc. gelatin
	cc. gelatin i.v.								500																	500						2800 cc. saline
	cc. saline s.q.		500			300														300				500	200	300		800			in 91 hr.
93	Hematocrit	44		43	40	40		45					45	42		39		40	42	40		44	44	49							1400 cc. blood
(35 lb.)	cc. blood i.v.		500			500										400															2300 cc. saline
	cc. gelatin i.v.																															in 53 hr.
	cc. saline s.q.		500			300							500				500					500									
94	Hematocrit	47		42			36	36	36		29				24	28		25		29	30		30	28	30	33	36				2000 cc. blood
(45 lb.)	cc. blood i.v.		500			500									500				500												500 cc. gelatin
	cc. gelatin i.v.											500																				2800 cc. saline
	cc. saline s.q.		500						500						300							500			500	500					in 72 hr.
95	Hematocrit	42		42			40	38	38			31			31		34	35		34	33	36		32	34	35	37	(resected)			2000 cc. blood
(40 lb.)	cc. blood i.v.		500			400								500													500				2400 cc. saline
	cc. gelatin i.v.																															in 72 hr.
	cc. saline s.q.		500							500									400				500		500						
97	Hematocrit	46		41			42		45	61			36		43		39	37		34		34	34	31	28	32	38	(resected)			2800 cc. blood
(22 lb.)	cc. blood i.v.		500			500			250					500							250				400		400				2800 cc. saline
	cc. gelatin i.v.																															in 72 hr.
	cc. saline s.q.		500						250										250		250					1200					
102	Hematocrit	40		41		40	43		38	42		40		32	43		40		39	40		38	32	39	39	37	28	41	41	43	2550 cc. blood
(27 lb.)	cc. blood i.v.		500						500					500									500			250	500				7000 cc. saline
	cc. gelatin i.v.																															in 100 hr.
	cc. saline s.q.		500				500					500		500				500					500		500	500	500	1000	1000	500	
103	Hematocrit	50		49		39		44	44	41		35		42		37															1500 cc. blood
(28 lb.)	cc. blood i.v.		500			500							500																		1500 cc. saline
	cc. gelatin i.v.																															in 26 hr.
	cc. saline s.q.		500			500				500																					
105	Hematocrit	50		45		44		48		45		49		46	53		54	49		51	48		50	46	44	47	45	48	50		2000 cc. blood
(32 lb.)	cc. blood i.v.		500			500			500				500																		4150 cc. saline
	cc. gelatin i.v.																															in 98 hr.
	cc. saline s.q.		00						500				500			500			800				500			550	300	300			

TABLE 3

Resume of Fluid Therapy in Ten Control and Ten Penicillin Treated Dogs

The total fluids received by the control dogs during their survival are compared to the fluids received by the penicillin treated dogs for equal periods of time. To do this each group was listed as in Chart I in the order of increasing survival time. Each control was paired with its corresponding penicillin treated dog (1 and 1, 2 and 2, 3 and 3, etc.). It can be seen that the amounts administered to each group in equal periods of time were essentially similar.

TYPE OF FLUID GIVEN	AMOUNT FLUID GIVEN TO 10 CONTROL DOGS	AMOUNT FLUID GIVEN TO 10 PENICILLIN TREATED DOGS
	cc.	*cc.*
Blood	12,100	13,950
Gelatin	6,050	3,000
Saline	12,350	12,950
Total	30,500	29,900

dogs the chloride at or just before death was either within the normal range or above it. In a few additional dogs other determinations were made. These are listed in Table 4.

It can be seen that the non protein nitrogen just before death, as expected, was elevated; also that the phosphorus and potassium values were high and that the carbon dioxide combining power was low. The sodium values were also above the normal range.

The nature of the peritoneal fluid in strangulated obstructions. Bloody peritoneal fluid was taken from two dogs treated with penicillin, at seventy two hours and at ninety eight hours respectively. The total protein of this fluid after it was centrifuged was 4.88 grams per cent in the first case and 6.13 grams per cent in the second. The hematocrit values for this fluid were 12 and 15 respectively, and the chloride values were 107.1 and 135.3 meq. perliter.

IV. Bacteriological Studies

In all dogs to be treated with penicillin cultures were made of the intestinal tract at operation as described previously. At autopsy which was performed immediately after death in all dogs in the series, cultures were taken from the intestinal tract above the site of the obstruction, of the peritoneal fluid and of the heart blood. In each

culture each organism was isolated and identified by the standard procedures in use at this hospital.

Escherichia coli, *Streptococcus faecalis*, *Staphylococcus aureus* and *Clostridium welchii* were the organisms most frequently encountered in the intestinal tract. *Pseudomonas aeruginosa* and *Proteus vulgaris* were also occasionally grown. Rarely one organism would overgrow the others to produce a pure culture. At death, in the dogs treated with penicillin the same types of organisms were grown from the

TABLE 4

*Blood Chemical Studies**

DOG	TOTAL SERUM PROTEIN	SERUM NPN	CALCIUM	PHOSPHORUS	SODIUM	POTASSIUM	CO_2
	Normal						
	5.0–7.0	25–38	10–11.5	3–4	138–145	3–5	23–29
	gm.%	mgm.%	mgm.%	mgm.%	meq./liter	meq./liter	meq./liter
96 C	4.88	63	8.6	12.5	155.0	9.0	10.3
99 C	4.06	54	7.5	8.9	165.0	4.3	12.8
101 T (31 hr.)	4.88	80	10.1	13.3		11.5	23.3
105 T (98 hr.)	6.19	65	11.6	14.8	159.0		13.2
	Alb. 3.19						
	Glob. 3.00						
106 T (33 hr.)	6.13	75	11.4	17.8	165.3	12.66 (hemolysis)	10.7
111 C							
(10 hr.)	5.25	33	10.6	3.6	146.5	3.2	25.4
(24 hr.)	6.00	35	9.3	4.7	156.7	3.7	18.3
(Survival 32 hr.)							
113 C							
(10 hr.)	5.00	30	10.3	5.7			23.3
(24 hr.)	5.25	33	10.5	4.5	142.8	4.3	20.4
(Survival 36 hr.)		55	9.9	10.0	169.0	8.5	9.9

* Dogs #111 and 113 were control dogs which are to be mentioned in a subsequent report (8).

intestinal tract that were present at the time of operation. The peritoneal cultures were often negative during the first twenty four hours whether or not the dogs were treated with penicillin, unless perforation had occurred. The heart blood was sterile in every dog, control and treated, except dog #103. Terminally the temperatures

of three treated dogs studied did not rise as compared to the terminal elevations to 105° in three of five controls in which the temperature was studied.

The prolonged survival time of the dogs treated with penicillin would indicate that penicillin in massive doses inhibits, at least temporarily, the action of the intestinal bacteria present. Eventually in the presence of the necrotic intestinal wall, the bacteria are able to overwhelm the host. It would seem probable that penicillin would be more effective in intestinal obstructions in which the degree of strangulation was less marked than in these experiments; especially since in previous experiments with non-strangulated closed loops (1) the animals were protected by penicillin for much longer periods of time.

MECHANISM OF SHOCK IN STRANGULATED OBSTRUCTIONS

In 1936 McIver (9) wrote that the "reduction of blood volume (in obstructions characterized by interference with the mesenteric circulation) by the transudate of plasma and fluids into the intestine and by stasis in the capillaries and mesenteric vessels may play a role in the symptoms and death. The importance of this factor probably increases in proportion to the length of bowel involved." Scott and Wangensteen (10, 11, 12) demonstrated that in obstructions in which there was interference with the venous side of the mesenteric circulation, blood loss through the resulting hemorrhagic infarction resulted in shock and death. The increase in weight of segments of intestine the veins to which had been tied was found in their experiments to average around 283 per cent. They calculated the average blood loss in these dogs to be 55 per cent. The strangulated bowel in our experiments also increased greatly in thickness and weight, due to the accumulation of blood within its wall. The inability of blood which is pumped into the bowel wall under arterial pressure to escape via the occluded mesenteric veins results in an elevated capillary blood pressure with consequent capillary rupture and hemorrhage into the bowel wall. Soon this hemorrhage extends through the bowel wall and into the bowel lumen and the peritoneal cavity. Part of the blood which escaped into the bowel lumen in our experiments was lost in the vomitus. The fact that bleeding, in our studies, continued for at

least forty hours as indicated by hematocrit readings is explained on the basis of the distention and vomiting resulting from the complete blockage of the bowel lumen. In all dogs there was between five hundred and two thousand cubic centimeters of peritoneal transudate having a hematocrit of around fifteen and a total protein content similar to that of blood serum. The values for chloride content of this fluid were similar to those for the chloride content of the blood.

Eighteen direct measurements of systolic blood pressure in various dogs indicated the presence of postoperative shock in most of the dogs studied. In dog # 102, which survived one hundred hours under penicillin therapy, the systolic blood pressure fourteen hours after operation was eighty-five. In dog # 103 the systolic blood pressure eight hours after operation was fifty five. The degree of shock in the various dogs and their ability to tolerate a reduced circulating blood volume certainly varied as indicated by the fact, for example, that a control dog living thirty five hours had the following blood pressure recordings, one hundred and thirty mm. of mercury at twenty hours after strangulation, one hundred and twenty seven at twenty seven hours and one hundred and twenty seven at thirty one hours. The blood pressure two hours prior to death was one hundred and ten. In addition to the routine postoperative transfusion given each dog, three other half liter lots of whole blood plus gelatin and saline were kept in readiness, and were administered as we thought necessary depending on the dog's hematocrit and general condition. As can be seen in Table 3 showing fluid administration, the amounts of fluid given both groups of dogs were similar. We cannot say with certainty that shock was not an important factor in the deaths of some of the dogs, especially those dying in under twenty hours.

These studies and the studies of Scott and Wangensteen and others indicate the importance of hemorrhage and shock in strangulated obstructions. It is only after these factors have been obviated as adequately as possible that the precise role of bacteria can be studied. Regardless of the importance of hemorrhage and shock, however, it seems evident that a bacterial factor of major importance is instrumental in death resulting from strangulated intestinal obstructions since the survival time was prolonged by penicillin.

FIG. 2. (TOP) STRANGULATED LOW ILEAL OBSTRUCTION IN CONTROL DOG 84 (DIED IN 24 HOURS)

The proximal turned in end, in center of photograph, is intact

FIG. 3. (BOTTOM) STRANGULATED LOW ILEAL OBSTRUCTION IN PENICILLIN TREATED DOG 102 (SURVIVED 100 HOURS)

(Photographs by Miss Elizabeth Cone and Miss Ruth Cordish, Department of Art as applied to Medicine, Photographic Division.)

FIG. 4. (TOP) STRANGULATED LOW ILEAL OBSTRUCTION IN PENICILLIN TREATED DOG 102. CLOSE-UP VIEW WITH LOOPS PARTLY SPREAD OUT

FIG. 5. (BOTTOM) STRANGULATED LOW ILEAL OBSTRUCTION IN PENICILLIN TREATED DOG 95 (CURED AFTER RESECTION AT 72 HOURS)

DISCUSSION

As was stated in the introduction, two groups of observations seemed to demand the carrying out of this investigation. The first of these were the observations of the efficacy of antibacterial therapy in closed isolated loop experiments and in ileal lesions produced by interference with the mesenteric blood supply. The second group of observations were those dealing with the importance of the factors of strangulation and infection in the deaths of patients with intestinal obstruction as it is treated at present.

This investigation in which strangulated obstructions of the ileum were studied from the standpoint of the role of bacterial action in the production of "toxemia" and death, was designed to correlate the observations cited and to determine experimentally whether antibacterial therapy could have a beneficial effect in the type of obstruction so dangerous in man. Volvulus of the strangulated segment which occurred in two of the treated dogs (#93 and 94) and in one of the controls (#82) in this series, converted simple obstructions into closed loop obstructions so that we believe it permissible to include strangulated closed loop obstructions in this discussion of strangulated simple obstructions.

It can be seen in Fig. 2 that penicillin can prolong the lives of experimental animals having the type of strangulated obstruction chosen for this study. It can also be seen that this prolongation has a definite limit, at the end of which the treated dogs die. Whether this limit is set by 1) the final inability of the penicillin in the doses employed to control bacterial growth, 2) fatal alterations in metabolic processes and body chemistry, 3) the presence within the peritoneal cavity of necrotic strangulated bowel or 4) some combination of these factors, cannot be definitely settled on the basis of this study. All that can be said is that large doses of penicillin exert for a period of time a definite protective effect upon animals with strangulated obstruction. Later, the animal dies in spite of the use of penicillin in the dosage employed.

These studies demonstrate that bacteria play an important role in the "toxemia" and death in dogs with strangulated ileal obstructions. This study does not demonstrate, however, that bacteria or bacterial products are the only important lethal factor in death from intestinal

obstruction. The important role played by hemorrhage, shock, loss of chloride and water are well recognized. Further studies in which a more perfect sterilization of the bowel is established and in which the other above mentioned factors are thoroughly controlled will be necessary in order to evaluate the relative importance of each factor. The present experiments simply serve to demonstrate that the life of an animal with strangulated obstruction can be prolonged when penicillin therapy is added to therapeutic measures designed to combat hemorrhage, shock, chloride and water loss. These results should be applicable to all cases of strangulated intestinal obstruction in man, and in all cases in which strangulation cannot be ruled out preoperatively. In all series of human cases reported by advocates of conservative therapy, instances are to be found in which strangulation had been missed and in which peritonitis led to death. These incidents are important because they contribute greatly to the mortality rate reported by such authors (6). Certainly anti-bacterial therapy should not be used as another excuse to delay adequate surgical measures in cases of acute intestinal obstruction, but its use in these cases might be expected to further lower a mortality rate which is still too high, in spite of progress in relief of distension by intubation and suction and in fluid and electrolyte replacement therapy.

CONCLUSIONS

1. In experimental animals with strangulated (simple and closed loop) ileal obstructions life is prolonged for a significant but limited period of time by treatment with massive doses of penicillin, as compared to untreated controls when both groups are treated for hemorrhage, shock, water and chloride loss.

2. After a period twice as long as the survival time of the controls the strangulated bowel was resected in penicillin treated animals with complete recovery in the two instances in which resection was performed.

3. Aggressive anti-bacterial therapy is indicated in all cases of strangulated intestinal obstruction in man and in all cases in which strangulation cannot be ruled out preoperatively. *This should be an adjunct and not a substitute for early and adequate surgical procedures in such lesions.*

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INTESTINAL OBSTRUCTION: A STUDY OF TWO HUNDRED AND FOUR ACUTE CASES WITH REFERENCE TO THE POSSIBLE EFFICACY OF ANTI-BACTERIAL THERAPY

ROBERT J. CALIHAN, M.D., JOHN D. KENNEDY, M.D. AND ALEXANDER BLAIN III, M.D.

From the Departments of Pathology and Surgery of the Johns Hopkins Medical School and the Johns Hopkins Hospital

The mortality of acute mechanical intestinal obstruction is too high. Advances in methods of decompressing distended bowel, in electrolyte and fluid replacement, in more adequate treatment of associated shock and in improved surgical technique have combined to reduce this mortality of from sixty to seventy per cent (C. Jeff Miller, 1929 (1); van Beuren and Smith, 1916–1919 (2); Moss and McFetridge, 1923–1927 (3)) to from fifteen to twenty per cent at present (Leigh, Nelson and Swenson, 1940 (4); Schlicke, Bargen and Dixon, 1940 (5); Johnston, 1940 (6); Dennis and Brown, 1942 (7)).

This investigation was undertaken to determine the cause of death in cases of acute mechanical obstruction of the small bowel seen at this hospital in the past ten years. We were interested to know: (1) the rôle played by diminished viability of the bowel wall and infection in the death of these patients and (2) what field, if any, exists for chemotherapy in the treatment of these lesions. Under modern therapy the adjuvants in the surgical treatment of intestinal obstruction are not directed primarily at the problems of strangulation and infection.

Harper and Blain (8) showed that in dogs with closed, isolated, jejunal loops death is due to bacteria or their products, and that such animals could be protected with large doses of penicillin. Blain and Kennedy (9) treated dogs having strangulated low ileal obstructions with massive doses of penicillin and found that these dogs survived between two and three times as long as controls not treated with penicillin. They extended this study and with Calihan and Harkins (10) were able to successfully resect these obstructions in four out of five dogs at a period which was twice the survival of the control animals.

Sarnoff, together with Poth (11) and Fine (12) has demonstrated the protective effect of prophylactic sulfasuccidine in treating unobstructed bowel which has an impaired mesenteric blood supply. Although their studies do not have such an immediate practical application in treating

intestinal obstruction in man, they nevertheless demonstrate the important rôle of bacteria in such lesions.

If this present analysis shows that bacteria or their products are important in the death of patients with intestinal obstruction, then antibacterial therapy might logically be expected to have an effect in patients similiar to that in the experiments cited.

MATERIAL

We have investigated the clinical and autopsy records of the patients who have been treated surgically for acute mechanical intestinal obstruction of the small bowel at the Johns Hopkins Hospital for the ten year period, 1936–1945. All cases were proven at operation to be completely obstructed as evidenced by distended loops above and collapsed loops below the site of the lesion. No cases of external hernia were included. The classification of cases was as follows:

1. Simple mechanical obstruction: the lumen of the bowel was occluded by a fibrous band, by an inflammatory reaction adjacent to the bowel or by a foreign body within the lumen (two cases of gall stone ileus).
2. Volvulus.
3. Internal hernia: herniation into recesses of the abdominal cavity, hernia through congenital or operative defects of the mesentery and hernia under adhesions.
4. Intussusception.

Each of these groups has been subdivided into the following categories according to the vascular condition of the intestinal wall as described by the surgeon.

1. Satisfactory: There was no gross evidence of bowel wall damage.
2. Discolored: The bowel wall was markedly discolored but regained its usual color within a reasonable period of time after release of the obstruction.
3. Gangrenous: The bowel wall showed frank gangrene.

Although this investigation primarily was directed at correlation of the vascular condition of the bowel wall and infection with mortality, other factors of interest were tabulated. These are age incidence, duration of symptoms, site of obstruction, etiology and pre-operative x-ray films.

DATA

Type of Obstruction: Of the two hundred and four cases included in this study one hundred and sixteen were simple mechanical obstructions, twenty seven were cases of volvulus, thirty five were cases of internal hernia and twenty six were cases of intussusception. In the ten year period covered by this study there were also ten cases of acute mesenteric thrombosis, all of which died. These cases did not fulfill our fundamental criteria because the lumen of the bowel was not completely occluded and so were not included in this series. Such lesions have been discussed fully in the papers by Harkins (13) and others.

Age Incidence: Table 1 is a composite of the age incidence of the entire series. Mortality is herein expressed as rate per decade. The distribution of the various types of cases in the different decades is essentially similiar except, of course, for intussusception.

No cases of intussusception occurred during the first three months of life; twenty one of twenty six cases (eighty per cent) of intussusception occurred between the fourth and twelfth month. This table also shows that in two hundred and four cases there were forty one deaths, a mortality rate of twenty per cent. Because of the small number of cases, no particular weight should be attached to the mortality percentage for each decade.

Duration of Symptoms Prior to Operation: Table 2 shows the duration of symptoms prior to operation and the number of fatalities in each time unit. It will be shown later that in this series of different types of obstructions, there was no correlation between the duration of symptoms and the condition of the bowel wall as found at operation. This does not mean, of course, that the duration of the obstruction in an individual case does not influence the degree of strangulation.

Site of Small Intestine Where Lesion was Found: Table 3. The designation "small bowel" includes all of those cases in which the operative note did not specify the exact site in the small bowel where the lesion was found. Also designated under "small bowel" are two cases of volvulus in which there was torsion of the jejunum and ileum on the foot of the mesentery and two cases of internal hernia in which the jejunum and ileum had passed through large mesenteric defects.

Etiology of the Intestinal Obstruction: Table 4 depicts the probable etiology of the obstruction. One hundred and thirty cases were as-

cribed to post-operative adhesions. Among these, twenty eight cases (twenty two per cent) occurred in the first month after operation, twenty nine cases (twenty two per cent) occurred during the period from one to twelve months, and seventy three cases (fifty six per cent) later than one year post-operatively. In the eleven cases of internal hernia ascribed to all other causes in Table 4, five were herniations through post-operative mesenteric defects and five were herniations through mesenteric defects of congenital origin.

TABLE 1

Age incidence

YEARS	SIMPLE MECHANICAL	VOLVULUS	INTERNAL HERNIA	INTUSSUSCEPTION	TOTAL	DEATHS	MORTALITY RATE
							Per cent
0–10	8	5	0	23	36	6	17
11–20	5	3	2	0	10	1	10
21–30	23	4	6	0	33	4	12
31–40	28	3	5	2	38	5	13
41–50	21	2	8	1	32	6	16
51–60	19	6	7	0	32	10	30
61–70	8	3	5	0	16	5	31
71–80	4	1	2	0	7	4	59
					204	41	20

TABLE 2

Duration of symptoms and mortality

	HOURS							
	0–6	7–12	13–18	19–24	25–48	49–72	73–96	96–
Number of Cases	19	35	15	21	34	27	27	26
Deaths	4	5	1	3	8	10	3	7
% Mortality	21	14	7	14	24	37	11	27

TABLE 3

Site of the obstruction

TYPE	ILEUM	JEJUNUM	SMALL BOWEL
Simple Mech.	87	13	16
Volvulus	21	2	4
Int. Hernia	23	4	8
Intussusception	26	0	0
Total	157 (77%)	19 (9%)	28 (14%)

Pre-operative X-ray Films: Scout films were taken in sixty seven cases and in sixty two of these (ninety three per cent) dilated loops and/or fluid levels were seen. This emphasizes the invaluable aid of scout films in diagnosis.

TABLE 4

Etiology

TYPE	POSTOPERATIVE ADHESIONS	INFLAMMATORY ADHESIONS	ALL OTHER CAUSES
Simple Mech.	93	15	8
Volvulus	17	2	8
Int. Hernia	20	4	11
Intussusception	0	0	26
Total	130 (64%)	21 (10%)	53 (26%)

TABLE 5

TYPE	SATISFACTORY	DISCOLORED	GANGRENOUS
Simple Mechanical	100	10	6
Volvulus	11	4	12
Internal Hernia	24	5	6
Intussusception	14	6	6
Total	149 (73%)	25 (12%)	30 (15%)

TABLE 6

CONDITION OF BOWEL	AVERAGE DURATION OF SYMPTOMS	NO. OF CASES	NO. OF DEATHS	% MORTALITY
Satisfactory	63 hrs.	149	23	15%
Discolored	48 hrs.	25	6	24%
Gangrenous	50 hrs.	30	12	40%

Condition of Bowel Wall: Table 5 shows the number of cases of each type of obstruction classified according to the condition of the bowel wall. Table 6 shows the condition of the intestinal wall as related to the average duration of symptoms prior to operation and the mortality rate.

Tabulation of Fatal Cases: A summary of all cases in the series which failed to recover is tabulated. In some of the cases the cause of death is not altogether clear.

TABULATION OF FATAL CASES

UNIT NO.	A.R.S.	DURATION OF SYMPTOMS	CONDITION OF BOWEL*	DAYS P.O. DIED	AUTOPSY NO.	COMMENT
			I. Simple Mechanical Obstruction			
130880	60 W.F.	168 hrs.	S	6 days	17109	Coronary occlusion with infarction of posterior wall of left ventricle.
144157	53 W.F.	240 hrs.	D	18 hrs.	16027	Generalized peritonitis.
143587	51 W.M.	2 hrs.	S	25 days		Fecal fistula, peritoneal abscess draining through site of old hernia repair.
145214	24 C.M.	24 hrs.	S	12 hrs.	15924	Fibrinopurulent peritonitis.
100145	39 W.F.	48 hrs.	S	3 days	15573	Generalized peritonitis due to leakage at site where torn bowel was sutured.
110145	37 C.F.	12 hrs.	S	6 hrs.	15449	Extreme shock and "toxemia" following release of adhesions. Obstruction of lower ileum and terminal aspiration of gastric contents.
116220	57 C.F.	48 hrs.	S	10 days	15654	Fibrinous peritonitis and early lobular pneumonia.
319334	17 W.F.	360 hrs.	S	10 hrs.	18911	Necrosis of loop of ileum without peritonitis. Widespread lobular pneumonia.
71864	78 W.F.	48 hrs.	S			Died on operating table. Death attributed to spinal anesthesia.
172445	44 C.M.	216 hrs.	G	3 days	16419	Diffuse fibrinopurulent peritonitis.
111826	46 C.M.	72 hrs.	D	3 days	15403	Atelectasis and lobular pneumonia.
111804	47 C.M.	48 hrs.	S	4 days	15405	Lobular pneumonia.
182958	26 W.F.	20 hrs.	S	5 days		Peritonitis. Six months pregnant.
61381	63 W.F.	192 hrs.	S	24 hrs.	14141	Fresh fibrinous peritonitis due to gangrene of the ileum. Early lobular pneumonia.

* The letter S, signifies surgeon's belief that the condition of the bowel was satisfactory at operation; D, that it was markedly discolored and G, that it was gangrenous.

TABULATION OF FATAL CASES—*Continued*

UNIT NO.	A.R.S.	DURATION OF SYMPTOMS	CONDITION OF BOWEL*	DAYS P.O. DIED	AUTOPSY NO.	COMMENT
I. Simple Mechanical Obstruction—*Continued*						
151479	10 W.F.	72 hrs.	G	99 days	16053	Purulent peritonitis with multiple abscesses and adhesions.
158763	47 C.F.	40 hrs.	S	7 hrs.	16149	Diffuse fibrinopurulent peritonitis. Ruptured tubo-ovarian abscess.
77242	28 C.M.	72 hrs.	S	5 days	15190	Ileostomy for intestinal obstruction, post-operative distention. Purulent bronchitis and early lobular pneumonia.
347616	42 W.M.	72 hrs.	D	4 days	19413	Bowel remained distended post-operatively in spite of Levine tube but symptoms obscured by delirium tremens. Autopsy: perforation of ileum through small necrotic area and fibrinopurulent peritonitis.
324571	3 W.M.	17 hrs.	G	12 hrs.		Generalized peritonitis.
341870	73 W.F.	36 hrs.	G	6 days	19317	Fibrinopurulent peritonitis.
218800	35 C.F.	72 hrs.	S	2 hrs.	18685	Distended, strangulated and necrotic loops of intestine with extensive acute diphtheritic enteritis and fibrinous exudate on the peritoneal surfaces. Aspiration pneumonia.
277210	34 W.F.	48 hrs.	S	20 hrs.	18119	Infarction of ileum. Pulmonary edema and confluent lobular pneumonia.
283214	47 W.M.	240 hrs.	S	2 days	18242	Organizing peritonitis due to clinically undiagnosed rupture of gall bladder with pericecal abscess.

TABULATION OF FATAL CASES—*Continued*

UNIT NO.	A.R.S.	DURATION OF SYMPTOMS	CONDITION OF BOWEL*	DAYS P.O. DIED	AUTOPSY NO.	COMMENT
			II. Volvulus			
122212	79 C.F.	24 hrs.	G	7 days	15555	Obstruction by kinking at site of resection. Multiple pelvic abscesses. Generalized peritonitis.
289022	62 W.M.	7 days	S	9 days		Myocardial failure.
254697	38 W.M.	3 hrs.	G	10 days		Generalized peritonitis.
285209	56 C.F.	4 days	G	50 days	254697	Organizing fibrinopurulent peritonitis.
66906	65 C.F.	5 days	S	5 hrs.	14577	Volvulus of lower one third of ileum and dilatation of proximal intestine.
16934	26 C.F.	3 days	G	40 hrs.	14112	Generalized fibrinopurulent peritonitis.
139379	59 C.F.	12 hrs.	G	6 days	15852	Fibrinopurulent peritonitis about lateral anastomosis. Pulmonary edema, early lobular pneumonia.
165892	7 W.M.	2 hrs.	S	14 days		Peritonitis. Developed two fecal fistulae, one high and the other low.
			III. Internal Hernia			
185556	59 W.M.	4 hrs.	S	3 days		Heart failure.
321355	70 W.M.	8 hrs.	D	9 days		Coronary occlusion.
150325	75 C.F.	96 hrs.	S	12 hrs.	16045	Strangulation and necrosis of a two foot segment of obstructed ileum.
224910	59 W.M.	72 hrs.	S	6 days	17374	Fibrinopurulent peritonitis.
114735	59 W.F.	72 hrs.	G	3 days	16178	Generalized peritonitis. Infection about suture line of ileocolostomy.
310343	55 W.F.	24 hrs.	D	24 days	18845	Generalized fibrinopurulent peritonitis.
240098	70 W.F.	12 hrs.	S	30 hrs.		Cause of death obscure.

TABULATION OF FATAL CASES—*Concluded*

UNIT NO.	A.R.S.	DURATION OF SYMPTOMS	CONDITION OF BOWEL*	DAYS P.O. DIED	AUTOPSY NO.	COMMENT
			IV. Intussusception			
A21252	10 mo. C.F.	72 hrs.	D	14 hrs.	17531	Reduction of intussusception and ileostomy. Infarction of ileum. Intestinal distention.
A30425	10 mo. W.F.	60 hrs.	S	8 hrs.		Generalized peritonitis.
202368	6 yr. C.M.	48 hrs.	G	10 hrs.	16942	Aspiration of gastric contents after resection of necrotic bowel.

DISCUSSION

There were two hundred and four cases of acute mechanical complete obstruction of the small intestine in this series; the obstruction was demonstrated in all cases at operation. Whereas in selected cases of intestinal obstruction coming to this hospital intubation and conservative therapy is employed, the plan of treatment for the majority of the patients considered in this paper was essentially as follows.

After the diagnosis was made the stomach of the patient was lavaged and continuous suction on an indwelling tube was begun. Parenteral fluid, plasma, blood and saline were given as indicated by the patient's condition. Then he was taken to the general operating room and explored. It should be emphasized that although most of the patients were intubated, in general, operation was not postponed to relieve distention by suction on the indwelling tube.

There were forty one deaths in the series, an over all mortality rate of twenty per cent. Half of these deaths, twenty three, were due to peritonitis. Peritonitis was the cause of death in one other case but this occurred after an elective operation to close an ileostomy and to perform an anastomosis forty eight days following the emergency procedure. One patient died of post-operative ileus. Three deaths were attributed to one of each of the following: a necrotic, strangulated loop, a fecal fistula and "toxemia". There were four cardiac deaths and four due to pneumonia and one due to aspiration immediately

following operation. One death was due to spinal anesthesia. By excluding these last ten deaths the corrected mortality is fifteen per cent.

Table 6 illustrates that, as might be expected, the mortality rate rises as the viability of the affected segment of the bowel wall diminishes. The decreased viability of the bowel wall enhances the activity of bacteria in infecting this segment and in passing through its wall to produce peritonitis. It should be pointed out also that the ability of bacteria to produce lethal toxins when proliferating in damaged bowel wall above an obstructing lesion, and to kill in the absence of peritonitis although questioned by many observers, is far from having been disproved. Therapy which has been shown to be effective against the effects of bacterial growth in intestinal obstruction in dogs, should be equally effective in human cases of intestinal obstruction in which strangulation is either imminent or present. Contrary to general belief regarding the resistance of the colon bacillus and other organisms to penicillin, the experiments cited in the introduction of this report, as well as those of Fauley, Duggan, Stormont and Pfeiffer (14) in which peritonitis due to gangrenous appendicitis in dogs responded dramatically to penicillin therapy, demonstrated that large doses of this antibiotic confer protection *in vivo* against such organisms.

Most physicians would probably agree to a trial of penicillin as an adjuvant in strangulated obstructions but there may be some who might say that the use of penicillin in non-strangulated cases would be a waste of penicillin. We feel that this objection is invalid because of the difficulty and inaccuracy of making the differential diagnosis. It is well known that the diagnosis of strangulation early in its course is most difficult. Table 6 shows that the degree of strangulation and altered viability of the bowel wall as found at operation were not related to the duration of the symptoms of intestinal obstruction. This same observation was also made by McKittrick and Sarris (15) in their study of 136 similiar cases at the Massachusetts General Hospital. They stated that they were unable to accurately diagnose early cases of strangulation and recommended immediate operation in any case of acute mechanical obstruction of the small bowel seen within twenty four hours after the onset of symptoms. Similar views are also held by Dr. Harvey B. Stone (16) and others with vast experience in this field. Certainly the duration of the symptoms cannot be used as a criterion in the differential diagnosis.

In the papers by some of the proponents of conservative therapy who claim to be able to differentiate strangulation there can be found incidents where strangulation had been temporized with disastrous results. The burden of responsibility therefore rests on the surgeon who attempts to make this early differentiation and finds after an interval of conservative therapy that his patient has a strangulated obstruction. The incidence of strangulation in this series and in other series is highly significant. McKittrick and Sarris (15) found strangulation in thirty-three per cent of one hundred and thirty six cases; Schlicke, Bargen and Dixon (5) found strangulation in thirty three cases (twenty six per cent) in a series of one hundred and sixty six cases treated at the Mayo Clinic. In our series of two hundred and four cases, fifty five (twenty seven per cent) showed strangulation with marked discoloration or gangrene at operation. In five additional cases although the condition of the bowel was described as satisfactory at operation, autopsy revealed strangulation and necrosis (a total percentage of around thirty). In twenty two of the forty one deaths in this series strangulation demonstrated either at operation or at autopsy was the direct cause of death or an important contributing factor. These cases accounted for over half of all instances in which there was peritonitis. Our study confirms the statement of McKittrick and Sarris that "strangulation is the most important single factor in determining the outcome of a case of acute small bowel obstruction."

SUMMARY

In this study of two hundred and four cases of acute mechanical obstruction of the small intestine proven to be complete obstruction at operation, there were forty one deaths, a mortality rate of twenty per cent. By excluding the cases in which death was not due directly to the intestinal obstruction (death due to cardiac failure, pneumonia, aspiration and death during spinal anesthesia) the corrected mortality rate was fifteen per cent. Peritonitis was the greatest single cause of death, fifty five per cent. The experimental work of Blain and Kennedy in which massive doses of penicillin prolonged the lives of dogs with strangulated obstructions, and the studies of Blain, Kennedy, Calihan and Harkins in which such dogs could be cured by resection at a period which was twice the survival time of control dogs not treated with penicillin have been cited. This would seem to indicate that peni-

cillin may serve a similiar useful purpose in strangulated intestinal obstructions in man.

CONCLUSIONS

1. Reasons are presented for clinical trial of massive doses of penicillin in cases of acute complete mechanical obstruction of the small bowel in man.

2. Penicillin is suggested as an aid to sound surgical therapy and not as another adjuvant with which to temporize in the treatment of acute mechanical intestinal obstruction.

We are indebted to Miss Blanche Pooler and the Record Room Staff for their cooperation during the course of this study.

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THE LOCATION OF THE CONSCIOUS CENTER IN THE BRAIN—THE CORPUS STRIATUM

WALTER E. DANDY, M.D.[1]

In 1930 the writer reported a remarkable cerebral phenomenon that followed resection of the left frontal lobe with the remains of a bilateral frontal glioma: (the right frontal lobe and its contained tumor had been extirpated three weeks earlier with no untoward effect). Immediately after the second operation there was almost complete absence of conscious effort for a period of seventeen days when she died of pneumonia. This patient lay with her eyes open or closed, never changed position, never spoke or responded in any way. The only movement, except opening and closing the eyelids, was an occasional contraction of a hand or leg. From day to day there was no change whatever. Urination and defecation were involuntary; swallowing movements were present; there were attacks of vomiting and hiccoughing. Throughout this period there were frequent minor focal epileptic attacks involving an arm or leg and occasionally a grand mal seizure. There was no rigidity of the extremities. The reflexes were not increased: Babinski reflexes were usually negative but occasionally positive. Strong sensory stimuli would induce a mild contracture of the affected extremity; lesser stimuli had no effect. The eyelids closed when the cornea was touched.

At no time following operation was there intracranial pressure. The enormous defect created by the removal of both frontal lobes was insurance against pressure. Moreover, frequent taps of the defect revealed no pressure and finally, continuous drainage of the defect produced no change in the patient's response. Since there was never intracranial pressure to account for the loss of consciousness the explanation could only be that the conscious center of the brain had been injured directly.

At the time of the original report, it was clear that an area of the brain controlling consciousness had been affected and I assumed that the bilateral ligations of the anterior cerebral arteries were responsible. And since the right anterior cerebral artery had been sacrificed many times without effect, I assumed that the left anterior cerebral arterial supply was probably responsible. A few years later Poppen (1939) en-

[1] Dr. Dandy died on April 19, 1946.

countered the same phenomenon in a patient following ligation of both anterior cerebral arteries. Poppen, too, supposed the vascular loss to be responsible but he was puzzled because he had had a series of three other cases in which both anterior cerebral arteries had been ligated without the same effect , in fact without any effect whatever. He also stated that in seven additional cases the left anterior cerebral artery had been ligated without any disturbances of consciousness. He also included a statement that in a series of ten cases the left anterior cerebral artery had been ligated at the Mayo Clinic without subsequent disturbance. Poppen concluded, after a suggestion by Fulton, that if the blood pressure was low at the time of the ligation, the loss of consciousness would follow, but if the blood pressure was not low, loss of consciousness would not result. In 1941 Poppen reported two more cases in which the low blood pressure had been elevated by transfusion before ligating the left anterior cerebral artery and nothing happened. He attributed the absence of effect to the elevated blood pressure resulting from the transfusion, although the same procedure had been harmless in several earlier cases without this precaution. I know of no other clinical reports of this immediate, total and permanent abolition of consciousness following operation.

Poppen was quite correct in stating that either one or both anterior cerebral arteries can be ligated without causing loss of consciousness. I have since ligated the left anterior cerebral artery a number of times and both anterior cerebral arteries (at the genu of the corpus callosum) in at least six cases without any noticeable disturbances related thereto and with no effect on consciousness. The total abolition of consciousness cannot, therefore, be explained by the loss of circulation to the brain beyond the ligated artery or arteries. However, there is now evidence in case 6 that this vascular occlusion, whether single or bilateral, is responsible for this loss of consciousness, but in a manner entirely unsuspected by either Dr. Poppen or myself. The explanation is a retrograde thrombosis of the anterior cerebral artery from the point of coagulation of one or both torn vessels to the internal carotid artery and including the recurrent medial striate artery (Heubner) en route. If unilateral this is the exact equivalent of ligating the anterior cerebral at the carotid and again at the anterior communicating artery, and, therefore, preventing collateral circulation to the medial striate artery

which supplies part of the corpus striatum. If bilateral thrombosis occurs it is the equivalent of tying both anterior cerebral arteries at the internal carotids.

It wou.d appear that Poppen's suggestion that a low blood pressure at the time of the ligations might lead to this loss of consciousness, may well be a very astute observation conforming to this concept, but also in a manner that he did not conceive. The low blood pressure per se could not cause this phenomenon but it is a well known fact that vascular thromboses, though always capricious, are precipitated by low blood pressure and particularly in defective vessels.

Although all of the brains in our series were inspected post mortem, still a thrombosed vessel would hardly be recognized unless one's attention was especially directed to it. Indeed in case 6 the thrombosed medial striate branch of the anterior cerebral artery was missed by myself and found by Mrs. Padget (Miss Hager) who made the drawings.

A note concerning the effect of anterior cerebral ligations should be entered here. All of the bilateral ligations of this vessel by Poppen and myself have been at the genu of the corpus callosum, the vessels being injured during resections of one or both frontal lobes; at this point these vessels lie very close together. The brain supplied by these vessels beyond this point is now known not to be important and no function is lost by their elimination. Ligation of a single anterior cerebral artery at its origin from the internal carotid would produce no ill effects because the collateral circulation from the opposite side (through the anterior communicating artery) would immediately restore the circulation. Below the anterior communicating artery it would be necessary (in man) to ligate both anterior cerebral arteries at the internal carotid artery to abolish the collateral circulation of these vessels. In one of our cases both anterior cerebral arteries were ligated alongside the internal carotid and identically the same loss of consciousness followed.

In the fifteen years since the original report, I have encountered nine additional cases in which this phenomenon—(immediate and permanent loss of consciousness) has followed operations for the removal of tumors or aneurysm (1 case). In one (Case 1) both frontal lobes were extirpated, both anterior cerebral arteries being ligated at the genu of the corpus callosum. In six (Cases 2, 3, 4, 5, 6 and 7) only the right frontal lobe was extirpated, but in each instance both anterior cerebral

arteries were ligated at the genu of the corpus callosum. In two (Cases 8 and 9) tumors were dissected from the third ventricle (one recurrent) and without injury to the anterior cerebral arteries, and in one (Case 10) both anterior cerebral arteries, were ligated (clipped) alongside the internal carotid arteries in order to stop bleeding when an aneurysm ruptured during its dissection. In two of the cases, therefore, the anterior cerebral arteries were not injured and precisely the same immediate and total loss of consciousness appeared. In all of these cases intracranial pressure was known not to be the cause of loss of consciousness. Necropsies were obtained in all, but, unfortunately, all except two of the brains (Cases 9 and 10) have since been thrown away and studies of the pathological material are, therefore, not now available. In Case 7, microscopic studies were not made but the gross specimen was carefully studied before the brain was lost. Until quite recently we were content to believe that the loss of the anterior cerebral arteries explained the loss of consciousness and our attention was not directed toward the basal ganglia, where the real disturbance occurred. In Cases 9 and 10 the brains have been carefully studied. In every case the total loss of consciousness and of voluntary effort were observed immediately after the time (four–six hours) when there could be no question of any effects of anaesthesia (avertin and supplementary ether, and in Case 1, ether alone.)

Case (1) H. M. patient, an obese woman, aged 51, was admitted to the Johns Hopkins Hospital 10/31/27 (surgical history no. 15048, Path. no. 10170). She was transferred from a psychopathic hospital where she had been an inmate for six weeks because of amnesia, complete disorientation and confabulation. The first sign of organic trouble was a series of eight convulsions four years ago. These occurred soon after the death of her mother by which she was greatly overcome; she was then in the menopause. During the next year there were no convulsions but she complained of severe headaches and showed marked changes of personality; she became untidy about her person and housework. Since then her headaches and personality changes had progressed. Her memory failed and her word was unreliable. After a stay of three weeks at the Sheppard Pratt Hospital a diagnosis of brain tumor was made.

Neurological examination revealed only bilateral papilloedema and pronounced mental changes. Ventriculography 11/1/27: left frontal tumor.

Operation 11/1/27: Excision left frontal lobe; tumor extended across the midline into the right frontal lobe. Weight of tumor and left frontal lobe was 105 grams.

It is interesting that within two weeks after the operation, her mental condition had cleared greatly.

Second operation 11/25/27: Resection right frontal lobe with tumor. The tumor reached the surface of the frontal lobe; it therefore passed all the way through both frontal lobes. The tumor had attached itself to the falx and a segment of this was excised. The weight of the frontal lobe and tumor was 103 grams. Both anterior cerebral arteries were ligated; this was later confirmed at necropsy.

Pathological diagnosis: Spongioblastoma multiforme (glioma).

Postoperative state: Patient lived seventeen days. Throughout this time she lay motionless except for an occasional grasping movement of the hands, and an occasional movement of the feet—both in response to stimulation but never in response to command. Her eyes would open and close, but never in response to command. Only once did the eyes follow anyone in the room; on this occasion the arm was strongly flexed during a test and the eyes turned to that side. It was, in fact, the only time her eyes were seen to turn from the forward position. There was never an attempted movement to change the position of the body. There was involuntary urination at intervals and stools were involuntary. There were not infrequent tremors, and fairly frequent convulsions, involving various parts of the body singly, at times one entire side of the body, and there were a few generalized convulsions. Occasionally the jaws would grind. Hiccoughing, grunting, sighing, vomiting, moaning, moving the tongue, occurred from time to time and on at least one occasion she spat out mucus. The pulse was rapid—100 to 150 throughout, respirations varied greatly but were regular and on the whole faster than normal—20 to 40. The temperature was elevated and irregular throughout—100 to 103, until the onset of the terminal pneumonia. All extremities were flaccid throughout, never spastic. The Babinski reflex was positive bilaterally; the knee kicks were normal. The pupils reacted to light directly and consensually.

The following note was made by Dr. Frank Ford 12/1/27: Patient is in deep coma, eyes closed, makes no spontaneous movements and does not respond to stimuli. Eyes move a little but non-concomitant and do not fix. Face does not move. Jaw partly open and does not move. Arms and legs are flaccid. When arm is pricked for vena puncture there is slight flexion at elbow. Strong stimuli of feet produce minimal flexion and feeble Babinski (bilateral); no ankle clonus. Tendon reflexes are active and equal and not increased. Passive rotation of head to either side causes no change in posture of arms or legs and no demonstrable tone. There are no signs of decerebrate rigidity.

Dr. L. F. Barker 12/7/27—12th day after operation—made the following note: The spontaneous movements recently have consisted of twitchings of both arms and legs, yawning and coughing. On passive movements of the left arm, she opened her eyes, turned them to the right and looked at me. A little later she turned her eyes up, but when the light was turned on she turned them forward again.

The pupils are approximately equal and react promptly to light. The mouth is slightly open. On pulling the right eyelid upward she closes the left eye and on elevating the left, the right eye closes. There is marked exaggeration of the deep reflexes in the right arm, but the biceps, triceps and periostial radials are not elicited on the left. There is, however, some tonicity of the muscles on the left arm. (The reflexes on other examinations were equal, active and not increased.)

The right k.k. is active, right ankle jerk hyperactive, the left k.k. present, left ankle jerk hyperactive. Babinski positive on right, not definitely elicited on the left.

The striking features are:—

1) Bilateral total paraplegia except for face and arm muscles.
2) Apparent bilateral anaesthesia.
3) Incontinent of urine and faeces.
4) I cannot be sure of vision, but I get the impression that she looked at me.
5) On clapping hands over ear, she looked at me.
6) Cannot test for aphasia, agraphia, or agnosis.
7) Some signs of motor irritation (twitching of upper motor extremities and last night a generalized convulsion).

Impression:—One gets the impression that the complete akinesis is associated with a total loss of spontaneous motor impulse. There may also be an absence of thought activity—patient lying as though in a catatonic stupor. There are no imperative expressive movements of laughing, crying or fright reactions. There is no way of testing affectivity but the patient shows no signs of affective reactions.

Remarks: Following the operation and for seventeen days thereafter there were no voluntary movements or responses, and only minimal reflex movements. At no time was there response to command. Both anterior cerebral arteries had been clipped at the genu of the corpus callosum. At that time the loss of conscious effort was attributed to these ligations, an explanation now known to be incorrect because several bilateral ligations of these vessels have been made at this point and without such effect. It should be emphasized that there was never intracranial pressure following the operation. The huge bilateral space resulting from the bilateral frontal lobectomy precluded intracranial pressure. Moreover, for several days after operation a flanged needle inserted into the frontal lobe, permitted constant drainage of the cerebrospinal fluid. Although this was unnecessary it gave further proof that there could be no intracranial pressure. Cessation of drainage produced no change in the patient's reactions and subsequent punctures of the intracranial space revealed no pressure.

Case (2) B. Z. white, male, age 37, History no. 130330; Path. no. 15698. Operation 2/5/38: Removal right frontal lobe with tumor (calcified) that extended into left frontal lobe. Much of left frontal lobe was also removed with the tumor. Weight of tumor and frontal lobes 211 grams. Both anterior cerebral arteries were thrombosed with the electro cautery.

Postoperative: Patient lived two days, never regaining consciousness; numerous

convulsions, tonic and clonic; all were mild. Swallowed, hiccoughed; slight movements of extremities; no reaction to painful stimuli. No intracranial pressure; repeated taps of the big frontal defect yielded clear fluid under no pressure.

Necropsy: Both anterior cerebral arteries occluded 2 cm. distal to the anterior communicating artery. Death from pulmonary oedema.

Case (3) D. K., white, male, aged 13, Hist. no. 198213, Path. no. 16896. Operation 4/24/40: Removal large hypophyseal tumor after resection of right frontal lobe: Both anterior cerebral arteries were coagulated at the genu of the corpus callosum. Weight of tumor 15.5 grams. Weight of frontal lobe 61.5 grams.

Postoperative: Lived five days. Never regained consciousness although no intracranial pressure. Hiccoughs frequent, many light generalized convulsions. Slight movements of extremities. No effort to turn in bed. No reaction to painful stimuli. Yawned, gritted teeth, voided involuntarily.

Necropsy:—Both anterior cerebral arteries closed, 1.5 cm. distal to the anterior communicating artery. Death from pulmonary embolus. Tumor extended into posterior cranial fossa, imbedding basilar artery to middle of pons.

Case (4) N. G., white male, age 55, History no. 20791. Path. no. 16999. Operation July 18, 1940—Air injection. Removal right frontal tumor—glioma. Tumor bilateral, both anterior cerebral arteries were coagulated when an attempt was made to remove the remaining tumor on the other side. It was predicted that he would not awaken and he did not. Fifteen hours later wound was reopened and some necrotic tissue was evacuated but there was no change in his condition.

Died three days later without response. Vomited twice, twitching left hand, moaned, hiccoughed, coughed and sighed. Voided involuntarily.

Necropsy: Both anterior cerebral arteries were coagulated 2 cm. beyond the anterior communicating artery.

Case (5) E. C., white male, age 26, History no. 224686; Path. no. 17409.

Operation 2/24/41; Ventriculography; resection right frontal lobe, and extension of tumor into left frontal lobe. Both anterior cerebral arteries were coagulated. Frontal lobe and tumor weighed 121.9 grams.

Postoperative: Patient lived fifty-one days; at no time was there any response. There were occasional slight movements of the right arm and the leg, never purposely. The eyes opened and closed but never in response to command or stimuli. Groaned and gnashed teeth occasionally. Occasional light convulsions, both tonic and clonic. Yawned and sighed from time to time. At times his eyes appeared to follow persons moving about room but this was not certain. When a light was thrown in the eyes the eyelids closed but there was no additional movement. The knee kicks were slightly hyperactive; Babinski negative bilaterally. Slight reaction to very painful stimuli.

Necropsy: Both anterior cerebral arteries were coagulated 2 cm. distal to the anterior communicating artery.

Case (6), H. L., white female, age 46: History no. 321320; Path. no. 18980.

Patient was operated upon 5/17/44 for a large dural meningioma of the olivary eminence. The intracranial pressure was so great that removal of the tumor was impossible without resection of the right frontal lobe. The tumor was so hard that its interior could not be curetted to reduce its bulk. The mass was enucleated with the finger; it weighed 17.7 grams. The frontal lobe weighed 94 grams. In removing the frontal lobe both anterior cerebral arteries were torn and coagulated over the genu of the corpus callosum.

Postoperative response: Patient did not rouse following operation and never reacted to any verbal stimuli. She hiccoughed, vomited, coughed and gagged and responded by slight movements of the hands to painful stimuli. She began menstruating on the third postoperative day. Urination and defecation were always involuntary. On the third day the wound was reopened. There was no intracranial pressure, no bleeding, and only a little necrotic tissue from the frontal resection; a large defect remained and was filled with clear fluid. The pulse constantly ranged from 110 to 130; the temperature was 101 to 103 and respirations 24 to 36 throughout the postoperative duration of life. She died of pneumonia 15 days after operation.

Necropsy: Verified the double ligation of these vessels at the genu.

Only the gross examination of this case can be presented. It was the first to draw our attention to the corpus striatum. On the right (operated) side, there was necrosis of the *lower half* of the anterior portion of the corpus striatum, fig. 1; the left was intact. This is the part of this structure supplied by the recurrent medial striate branch (Heubner) of the anterior cerebral artery. The anterior cerebral artery on this side was completely thrombosed from the point of ligation at the genu of the corpus callosum to the internal carotid artery and included the artery of Heubner. The thrombus was confirmed microscopically. On the left side there was a small thrombus at the point where the artery was torn; this ended 2 cm. above the anterior communicating artery, which was patent.

It is worthy of note that there was no trauma to the upper half of the corpus striatum on either this or the other side. The necrosis in the lower half (cross section) of the corpus striatum on the right was therefore due to occlusion of the anterior cerebral artery by a thrombus extending from the torn end of this vessel to the internal carotid artery. A similar extensive thrombus did not develop on the opposite (left side).

Case (7) C. C., white, male, age 40. History no. 365332. Path. no. 19635.

Patient was semiconscious and unable to answer questions. There was a history of bifrontal headaches for seven years. He had been bedridden for the past three weeks. His vision was said to have been poor. There was bilateral papilloedema but no haemorrhages. The deep reflexes were slightly more active on the left. Pulse was 50 per minute.

Operation 10/10/45: Ventricular air injection; 5 cc. of air were injected into the left ventricle, 10 cc. into right: The third ventricle did not fill. The right

frontal horn was depressed and dislocated to the right. Only the posterior and descending horns filled on left. Diagnosis: Bifrontal tumor, greater on left.

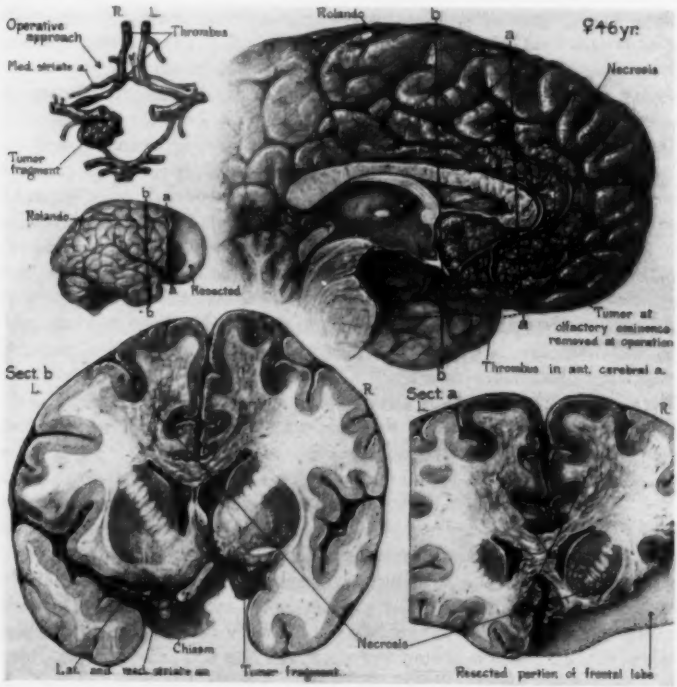

FIG. 1. Case 6. A large suprasellar tumor was removed after resecting the right frontal lobe to obtain an adequate exposure. A small fragment of tumor remained along the right carotid and posterior communicating arteries. Both anterior cerebral arteries were severed at the genu of the corpus callosum. The right anterior cerebral artery was thrombosed from the point at which it was torn at the genu of the corpus callosum to the internal carotid artery and the loss of the medial striate artery of Heubner was responsible for the necrosis in the right corpus striatum, and this in turn was responsible for the patient's failure to regain consciousness. Only a small thrombus was present at the site of the coagulation of the left anterior cerebral artery. Note the extent of the necrosis resulting in the frontal lobes from ligation of both anterior cerebral arteries. This patient lived fifteen days.

Since the tumor was apparently bilateral, it seemed preferable to attack the right frontal lobe first.

The right frontal lobe was widely resected; the weight was 132 grams. Both anterior cerebral arteries were occluded at the genu of the corpus callosum. A tremendous encapsulated dural meningioma lay under the falx; about three-fourths or more were on the left side, the remainder bulged to the right. It shelled out very easily and with scarcely any bleeding; the weight was 116 grams. A prompt recovery was expected but patient did not rouse. The first movements were: squeezing with right hand (not left) and scratching nose (10 hours after operation). During the next twenty-four hours there were fairly frequent movements of both hands and reflex gripping with both hands: clonic convulsions began 18 hours after operation and were fairly frequent thereafter: some were restricted to one arm or leg, others were generalized. There were also frequent tonic spasms of either or both arms and legs; at times the whole body became rigid. Very slight movements followed strong stimuli but no spontaneous movements after twenty-four hours. At no time after the operation was there any response to commands and no attempts to turn the body. At no time was there intracranial pressure: Repeated taps of the great bilateral frontal defect insured its absence. Death occurred thirty-three hours after operation.

Necropsy: Gross examination: Coronal sections (a, b, c, and d) have been made as shown in fig. 2. The injury to the corpus striatum is shown to be at the upper anterior end of the *right* corpus striatum (Section B and to a much lesser degree in Section C). Above the internal capsule in Section B, it has sloughed off.

Microscopically: There were many ruptured blood vessels, much haemorrhage, areas of marked oedema and swollen degenerated fibers in the internal capsule. The lower anterior and more inferior part of the striatum, which is frequently supplied by the medial striate branch of the anterior cerebral artery was not affected by the operative procedure except for some oedema and small haemorrhages.

Both anterior cerebral arteries had been injected with India ink after death and the circulation of the striate arteries were intact on both sides.

On the left side the corpus striatum showed some old foci of perivascular round cell infiltration (syphilitic?) and a few areas of slight oedema but no haemorrhage or necrosis.

The thalamus showed no gross change.

The hypothalamus was beyond the field of operation and showed no alteration in the gross.

Case (8) H. B., white female, age 17, history no. 44281; Path. no. 12771. Operation 9/9/32: Removal recurrent tumor third ventricle (glioma), (previous operation 7/13/32 with uneventful recovery). The tumor was adherent to the wall of the third ventricle and was removed by sharp and blunt dissection. No arteries were encountered. The approach was along the falx with retraction of the posterior part of the right hemisphere as in a pineal operation.

Postoperative: Following operation patient never made any response or conscious effort. There were slight movements of the arms and legs at times. She lay on the back and without any attempt to turn. She moaned, sighed, coughed, hiccoughed and was incontinent. There were frequent generalized convulsions,

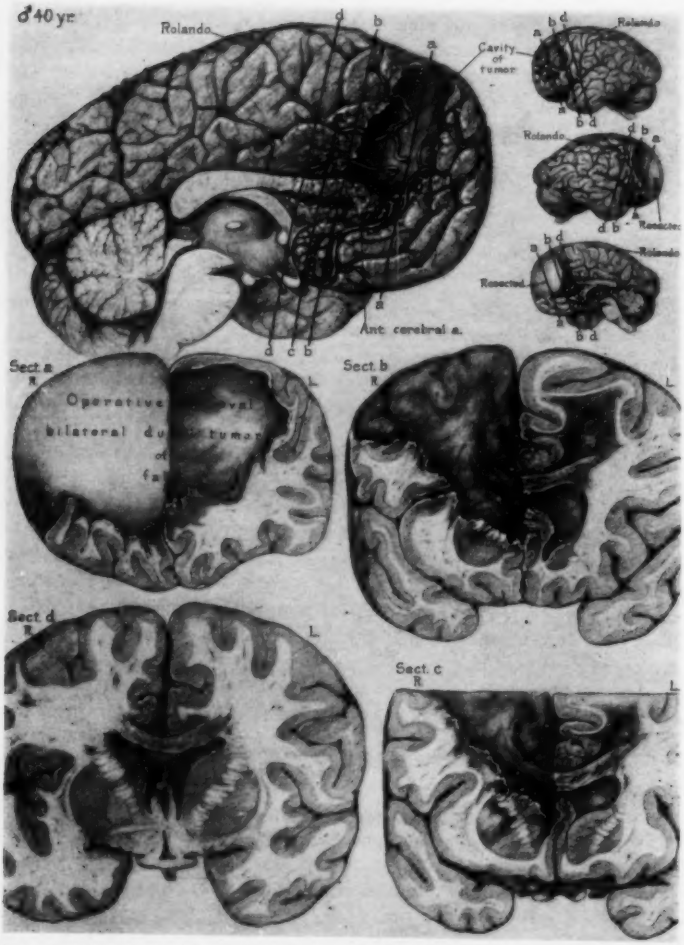

FIG. 2. Case 7. After resecting the right frontal lobe to produce adequate exposure a large bilateral dural meningioma was removed from the region of the falx. In the coronal sections (b), (c), and (d) there was necrosis in the upper half of the corpus striatum on the right side. The necrotic area had sloughed off in section b and was partially retained in section c. This did not include the thalamus. The necrosis was the result of direct trauma in the line of section of the frontal lobe. The location of the coronal sections is shown by the lines through the brain in the upper figure. This patient lived thirty-three hours.

also tonic attacks with rigidity of the entire body. She lived four days without change in the state of consciousness. The lateral ventricles were large and intracranial pressure was controlled by repeated ventricular taps.

Case (9) G. R., white, female, age 25: History no. 287888; Path. no. 18351.

Operation 4/5/43: Immediately after localization by ventriculography, an ependymoma was removed from the right lateral and third ventricles. Because the tumor was rather large and deeply placed it was necessary to remove the right frontal lobe to provide the proper exposure. The anterior cerebral artery was not injured. The removal of the tumor was followed by diffuse oozing from both the third and lateral ventricles; this was controlled by packing repeatedly and with some applications of the cautery. The tumor weighed 5 grams, the excised lobe 90 grams.

Postoperative Response: There was no return of consciousness at any time before death twenty-three days later. She yawned, coughed, hiccoughed, moved both hands on a few occasions, voided and defecated involuntarily. Never was there any response to questions and only slight movements of the arms or legs to painful stimuli. From time to time there were mild focal convulsions. There was never intracranial pressure. This was shown by repeated punctures of the cerebral defect.

Necropsy: Death from pneumonia. The anterior cerebral arteries were intact.

Case (10) J. H. M.: white male, age 28; surgical history no. 339857: Path. no. 19261.

Operation 12/22/44: Avertin and ether anaesthesia: A small arterial aneurysm of the right anterior cerebral artery was dissected until the neck of the sac was free. It ruptured when a defective clip holder cut the neck of the aneurysm. After an initial spurt of blood that quickly filled the wound, the spatula compressed the bleeding point and the wound was dry. The anterior cerebral artery on the left was seen and clipped and the neck of the aneurysm was coagulated with the electro-cautery. When the spatula was removed the bleeding had entirely stopped. The only trauma was at the site of the coagulation of the neck of the aneurysm.

Postoperative Responses: The first response was ten hours after operation when he moved right hand toward face. Fourteen hours after operation he would hold your hand reflexly; eyes were wide open but blank. Pulled at dressings. Fifteen hours: moved both hands to face. Eyes open and blank. Tried to vomit; hiccoughing. Seventeen hours; twitching of whole body—started in right hand. Twenty-two hours later: Pulse 160, temperature 105.4, respiration labored. The bone flap was removed; there was slight pressure; the brain barely protruding. His condition became steadily worse; death came forty-eight hours after operation.

Remarks: In this case the lack of conscious response was essentially the same as in other cases and was due to ligation of both anterior cerebral arteries at the internal carotids. However, the element of intracranial pressure cannot be entirely

subtracted from the picture; it would surely result in time from the reaction to necrotic tissue. It is my belief that signs of pressure could not have developed in the first twelve hours and during this time there were no signs of returning consciousness.

Necropsy: The brain was sketched from all aspects, sliced coronally, each section drawn and about twenty blocks made for microscopic study. The corpus striatum showed complete necrosis of the lower half (coronal section) on the right side and the lower third on the left. This differing quantitative distribution of necrosis conforms to the variability of the medial striate branches of the anterior cerebral artery, including the recurrent artery of Heubner. It will be seen in sections D and E of fig. 3 that the necrosis from the operative trauma at the base of the brain passes into the area of necrosis of the corpora striata of vascular origin and this terminates at the anterior border of the thalamus. This area of necrosis covers the anterior part of the hypothalamus but not the tuber cinereum or the corpora mamillaria. Microscopic section of this region through the hypophyseal stalk was free of oedema or necrosis.

The thalamus was not abnormal microscopically or in the gross.

ANALYSIS OF CASES WITH LOSS OF CONSCIOUSNESS

In all of the above cases, consciousness was totally lost immediately, did not return nor were there any signs of clearing, up to fifty-one days—the longest surviving period. In 6 of these cases death occurred within 5 days and in three of these within 2 days after operation. It cannot be said that consciousness was *permanently* lost in these cases. In four cases death occurred 15, 17, 23 and 51 days (Cases 6, 1, 9 and 5) and until the time of exitus there had been no sign of returning consciousness; in these, I have assumed the consciousness to have been permanently lost. There can be no doubt that a specific area of the brain controlling consciousness had been damaged and probably destroyed either directly or indirectly through deprivation of its blood supply. The only functions remaining were automatic.

From the results of extensive resections of the brain one can be certain that neither cerebral hemisphere above the basal ganglia plays any part in consciousness. This statement is based upon seven total *right* hemisphere removals that I have performed in man, another by Gardner and the single total removal of the *left* cerebral hemisphere by Zollinger. Moreover, while experiments in animals are not necessarily transferable to man, the famous Goltz's dogs with both cerebral hemispheres removed and with normal locomotion afterwards are at least

proof that consciousness is not affected by the absence of both cerebral hemispheres in dogs. There can, therefore, be no doubt that consciousness is not related to the cerebral hemispheres; it must, therefore, be referred to the basal ganglia or the thalamus, or possibly the hypothalamus or brain stem.

From the first seven cases in this report, this phenomenon of immediate, total and permanent loss of consciousness resulted from exactly the same procedure, i.e. resection of one or both (1 case) frontal lobes; however, in the bifrontal case, loss of consciousness followed removal of the second lobe i.e. the left frontal lobe had previously been removed with no effect. It has been shown at necropsy in each of these cases that both anterior cerebral arteries were severed at the genu of the corpus callosum. But since the deprivation of the blood supply of these vessels beyond this point is now known not to cause loss of consciousness, there must be another explanation for this phenomenon. Moreover, the part of the brain that is injured and is responsible for this change must be in the immediate environs of the line of section of the frontal lobe or lobes. There is only one part of the brain that could meet this condition i.e. the corpus striatum. One might suggest a second part of the brain i.e. the anterior part of the hypothalamus but this area lies at some distance from the line of the resection and is not traumatized, (except Case 10).

From the cases in this report three have been studied carefully at necropsy (two with microscopic studies) and all of these show sharply defined necrosis of the anterior part of the corpus striatum (the head of the caudate nucleus and the lentiform nucleus (the globus pallidus and the putamen).

In two of the cases (6 and 10) this necrosis was in the lower half of the tip of the corpus striatum and was due to loss of its blood supply from occlusion of the recurrent medial striate artery (Heubner). In Case 10 the necrosis was bilateral and followed ligation of both anterior cerebral arteries at the internal carotid arteries, following which necrosis follows because the arteries can receive no collateral. It has been shown by Ayer and Aitken (1907 and 1909), Beevor (1909), and recently Alexander (1942) that all the arterial supply to the basal ganglia is by end arteries. In Case 6 the right anterior cerebral artery (and its medial striate branch) was thrombosed from the point at which the artery was

occluded at the genu of the corpus callosum to the internal carotid artery and there was necrosis in the same area of the corpus striatum as in Case 10. Moreover, there was no trauma to the upper half of the corpus striatum; the necrosis was, therefore, of vascular and not traumatic derivation. It is very probable that other cases in this series have had similar extensions of the intraarterial thrombus, but without a careful study of the vessels and the basal ganglia, thromboses could easily have been overlooked.

In the remaining case (7) with postmortem study, the *upper* half of the anterior part of the corpus striatum was necrotic and had sloughed off. This was due to direct trauma that occurred in the line of the resection. This also was strictly unilateral and confined to the right (operated) side. The inferior half of the corpus striatum was oedematous but not necrotic. Whether the upper half, i.e. above the internal capsule, or the oedematous portion below was responsible for the loss of consciousness cannot be stated. The trauma was sufficiently severe to implicate the entire cross section of this structure from oedema.

Permanent loss of consciousness probably therefore results either from direct trauma to the anterior part of the corpus striatum or from deprivation of its blood supply. And since in two of these cases the necrosis of this structure was strictly unilateral, (and on the right side), one can only conclude that bilateral involvement is not necessary. Whether the same result would obtain from involvement of only the left side cannot be answered.

In none of these three postmortem examinations was there any gross change in the optic thalamus and in the two with microscopic studies there was none.

If Case 10 were alone, one could not exclude the possibility that the anterior portion of the hypothalamus might play a rôle as the conscious center because the traumatic necrosis includes this area (both anterior cerebral arteries were clipped at the carotids). However, in both Cases 6 and 7 the necrosis is far removed from the hypothalamus and there can be no doubt that its exclusion cannot be questioned.

Perhaps a word of explanation is in order concerning the plane of the resected frontal lobe. The usual incision passes through the lobe transversely in a line corresponding roughly with the fronto-parietal bony suture and is well in advance of the motor area, which it roughly

parallels. The incision through the lobe passes slightly forward and is usually just anterior to the genu of the corpus callosum. It should miss the anterior horn of the lateral ventricle, though not infrequently the tip of the ventricle is opened. At the base of the skull this would terminate about 2 to 3 cm. anterior to the olivary eminence. In more extensive resections of the lobe (dependent upon the posterior extent of the tumor), the incision in the cortex begins nearer the Rolandic area and in the depths the incision is curved forward in order to miss the corpus callosum and thus avoid the anterior cerebral arteries. It is in these more extensive resections that these vessels and the underlying part of the basal ganglia may be injured at the genu of the corpus callosum. Every effort is made to avoid tearing the branches of the anterior cerebral artery and thus avoid injury to the main trunks but this is not always successful; when torn the vessels are packed with wet cotton, then isolated and coagulated with the electro-cautery or occasionally silver clips.

LOSS OF CONSCIOUSNESS FOLLOWING EXTIRPATION OF TUMORS OF THE THIRD VENTRICLE

In two cases (8 and 9) precisely the same loss of consciousness—total and permanent—followed removal of tumors of the third ventricle (one recurrent). In neither of these could either anterior cerebral artery be injured (post mortem verification) because the operative approach is remote from these vessels. These two cases demonstrate that the same loss of consciousness results from injury of the basal ganglia directly and without injury to the vascular supply—i.e. the anterior cerebral arteries.

These cases do not, however, indicate whether the damage that caused loss of consciousness has been done anteriorly at the corpus striatum or posteriorly at the thalamus, or both. The preceding experiments (Cases 1 to 7) are necessary for the more precise identification of the area involved.

In this connection I have reviewed a series of 5 pineal tumors operated upon with fatal result; in all of these the tumor entered the posterior part of the third ventricle and the trauma of removal affected the thalamus rather than the corpus striatum. Upon coming out of the anaesthetic there was always immediate return of consciousness

with movements of all extremities. Later consciousness was lost as the postoperative oedema spread to the more anteriorly situated corpora striata. From comparison of these cases with those in which the basal ganglia are injured anteriorly, additional evidence is added that the conscious center is in the anterior part of the corpus striatum and not in the thalamus or the posterior part of the corpus striatum.

LIGATION OF THE ANTERIOR CEREBRAL ARTERIES

It has been stated that in two cases deprivation of the blood supply to the corpus striatum on one or both sides resulted in necrosis of the anterior part of the corpus striatum (of one or both sides depending upon whether one or both arteries are occluded.)[2] Although this is the general rule, in a certain percentage of cases variously estimated from $\frac{1}{4}$ to $\frac{1}{3}$ (Ayer and Aitken, Beevor, and Alexander), the anterior cerebral arteries send no branches to the corpus striatum: in these cases the blood supply is from branches of the middle cerebral arteries which (with the anterior choroidal artery) normally supply the remainder of the basal ganglia. It is evident, therefore, that elimination of the blood supply of one or both anterior cerebral arteries will not always be followed by necrosis of the corpus striatum; but that in $\frac{1}{4}$ or $\frac{1}{3}$ of cases in which the recurrent medial striate branch (Heubner) is absent, or very small, the anterior cerebral arteries may be sacrificed without effect upon the conscious area. It should, therefore, be emphasized that when cases of bilateral ligations of the anterior cerebral arteries at the carotids are subsequently reported to be done with impunity that the anterior cerebral arteries should be carefully inspected for these branches when necropsy affords an opportunity.

It should also be emphasized that ligation of one anterior cerebral artery at the internal carotid will not normally affect the corpus striatum because of the collateral circulation through the anterior communicating artery (occasionally the anterior communicating artery is absent).

LITERATURE ON THE CONSCIOUS CENTER

I know of no instances in the literature where total and permanent loss of consciousness described above has been described from any

[2] Loss of consciousness does not follow ligations of both anterior cerebral arteries in dogs or monkeys (unpublished experiments).

lesion of the brain or following any experiment. A considerable literature has accumulated concerning pathological sleep, which doubtless is concerned with the center of consciousness and is a physio-pathological disturbance of it or its connections. For many years a center for sleep has been placed in the environs of the third ventricle. This conclusion has been reached through pathological material—largely tumors, from the end results of encephalitis and more recently from experiments on animals.

Sinkler (1893) reported a tumor as large as a hen's egg in the posterior part of the optic thalamus; the patient had had recurring attacks of drowsiness but the size and location of the tumor might well have induced periods of sleep from intracranial pressure. Probably in most tumor cases somnolence is due to intracranial pressure: and tumors causing ball valve obstructions of the ventricular system are particularly prone to produce recurring attacks of somnolence because of the recurring blockage of the ventricles (hydrocephalus). For this reason many tumors of the cerebellum and third ventricle, and even of the lateral ventricles produce recurring attacks of sleep. In the presence of tumors it is, therefore, always difficult to subtract the element of intracranial pressure from the local effects of the lesion.

Luksch (1924) reported a postmortem study on a 27 year old patient who had had recurring attacks of stupor over a period of three weeks. She had a small metastatic abscess in the right thalamus and third ventricle; this abscess was a sequel of endocarditis. Fulton and Bailey (1929) collected a group of tumors of the third ventricle; in all their five cases there were periods of uncontrollable sleep. Their conclusion was that the region of the brain controlling sleep was in the thalamus and hypothalamus and possibly in the region of the Aqueduct of Sylvius. Globus (1940) reported two cases of intermittent, incontrollable drowsiness, both with extensive arteriosclerosis of the cerebral vessels and in each there was bilateral softening of the optic thalamus. Much the same localization was reached by Von Economo (1928) in studying brains from an epidemic of encephalitis. Penfield (1938) briefly mentioned a remarkable result in a patient from whom he had removed a tumor from the region of the pineal and with extension into the posterior part of the third ventricle. She was unconscious or nearly so for 6 weeks and finally recovered. It is not stated whether there were movements of the body and if so, how much. He concluded that

the center for consciousness, which had been injured, was in the optic thalamus. In the light of our present experiments it would now appear more probable that oedema of the contiguous corpora striata was responsible and as the oedema cleared, consciousness belatedly returned. Had the conscious center been injured directly and so severely, the loss of consciousness would doubtless have been permanent.

If the coma was total for 6 weeks in Penfield's case, the period of somnolence is surpassed in only one of our patients (5), who lived 51 days without change. I cannot say that consciousness might not have returned in some of those with shorter survivals. One can only say that there was no indication of improvement. In one of our recent cases there was loss of consciousness for 4 days, then gradual return of movements and consciousness and on the fifth day there was response to command. In this patient both anterior cerebral arteries had been ligated following bilateral removal of the frontal lobes for a bilateral glioma. It was assumed that the conscious area had been traumatized but not destroyed and that as the oedema subsided the conscious area again functioned very much as in Penfield's case, but with a more rapid recovery. A similar recovery takes place in recovery from traumatic injuries of the brain and also from coma during the last stages of intracranial pressure from brain tumors, after the pressure has been relieved. In all of these examples the conscious center must be affected but not to a point beyond repair.

From experiments on animals, Hess (1932–1936) was led to place the center for sleep in the same region, i.e. the thalamus and hypothalamus. He placed electrodes in the region of the hypothalamus and the thalamus and induced sleep by stimulation. Ransom (1939) produced lesions in various parts of the thalamus and hypothalamus, running the needle through from the surface of the brain and passing a current through for brief periods. Lesions in various locations resulted. His best results in terms of sleep were in the hypothalamus (although the needle passed through the basal ganglia). Spiegel and Maba (1927) on the other hand got differing results with similar methods and obtained greater sleep from lesions in the thalamus. Stimulation experiments could hardly localize a center with accuracy for the effect of stimulation would carry beyond the point stimulated. The lesions produced in the animal experiments would appear to be near but not at the actual

center for consciousness: if the center of consciousness were injured consciousness would be abolished as in our human cases.

SIGNIFICANCE OF "CONSCIOUSNESS"

There has been much discussion about the meaning of consciousness. If in its original sense consciousness implies the recognition and utilization of afferent impressions, the only way of recognizing consciousness is by the efferent manifestations of speech and motion. The definition is doubtless reversible, for if, with intact pathways of speech and movement, there is no outward expression of speech and movement, the assumption of recognition of incoming impressions could not be assumed and these functions are in all probability abolished also. In these cases practically all activities of the body (there are a few minor movements)[3] are lost except the autonomic—and that certainly means the loss of consciousness. The center for consciousness is, therefore, the "integrator" of all the voluntary activities of the brain. With the loss of this center the body becomes a vegetative organism. Doubtless it is this center of consciousness that is concerned with sleep. With its complete destruction there have been, of course, no periods of recurring sleep.

COLLATERAL FOLLOWING ARTERIAL LIGATIONS IN THE BRAIN

The collateral circulation that has maintained in very surprising degree the integrity of the frontal lobes that have been deprived of their circulation by ligation of both anterior cerebral arteries is interesting. This study is not concerned with the area of consciousness but is a secondary consideration. In Case 10 both frontal lobes looked surprisingly normal and were certainly not soft or necrotic (fig. 3). The microscopic study, however, did show oedema and spotty areas of necrosis throughout. In the right frontal pole near the operative site, there was fresh haemorrhage in the meninges, old and fresh haemorrhage around arterioles and many dead cells. More distally, about midway between the operative area and the Rolandic fissure, three sections showed relatively large areas of normal brain and irregular

[3] In none of the cases has there been an absolute loss of movement of the hands and feet but in all it has been within a fraction of totality. In cases 7 and 10 occasional movement of the hands to the face was a trifle more motor response than obtained in the remaining 8 cases.

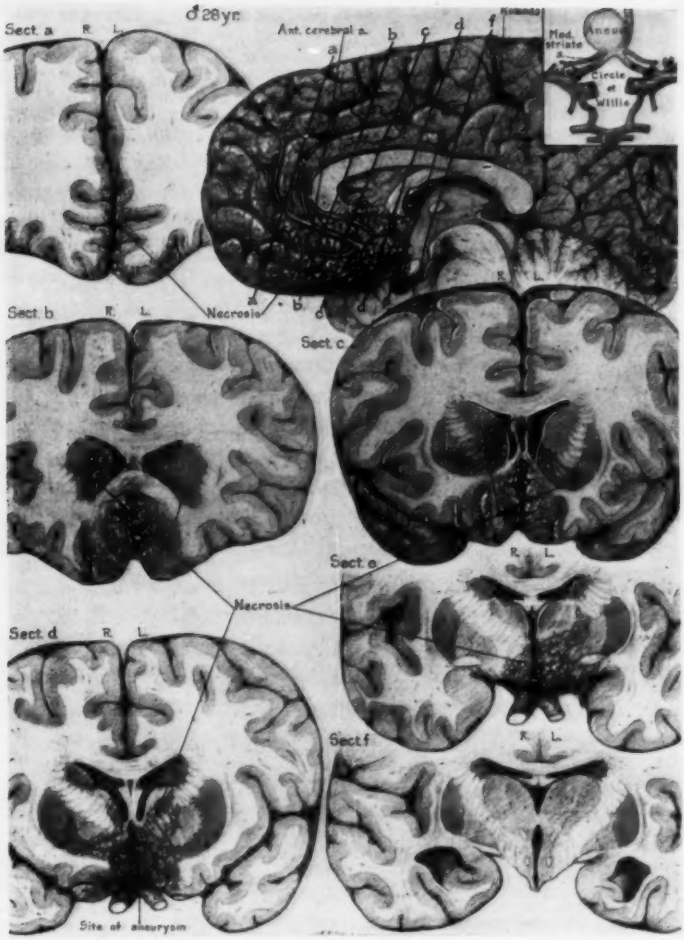

FIG. 3. Case 10. Following rupture of the aneurysm of the right anterior cerebral artery during the application of a defective clip to the neck of the aneurysm, the bleeding was controlled by a clip on each of the anterior cerebral arteries at the junction of the internal carotid arteries. Following this patient showed no signs of returning consciousness. The necrosis is in the distribution of the blood supply to the anterior and inferior part of the corpus striatus as shown in sections b, c, and d. There is also necrosis from trauma at the base of the frontal lobes; this extends to and is confluent with that in the corpus striatum, but it does not extend into the optic thalamus (sections e and f). The greater necrosis in the corpus striatum on the right than on the left is due to the variability found in the medial striate arteries. This patient lived forty-eight hours. Doubtless death was due to intracranial pressure resulting from the necrotic tissue, but this could hardly have arisen within the first twelve hours, during which time he was totally unconscious.

areas of necrosis. Reaching the premotor and motor cortex, there were still larger areas of normal brain and smaller foci of dead cells. In all sections little change was detected in the white matter.

The left cerebral cortex in the distribution of the anterior cerebral artery showed the same changes as the right (operated side) but to a definitely lesser degree. The section from the lower tip of the frontal pole, 4 cm. in front of the bed of the aneurysm, showed areas of necrosis and many haemorrhages, but 4 cm. more distally at the upper tip of the frontal pole there was little more than oedema. In each of two sections made 3 and 4 cm. in front of the Rolandic fissure respectively, there was found only one small focus of dead cells. Blocks taken from the motor and sensory cortex and including the gyrus cinguli on this side revealed perhaps a little oedema but no necrosis.

In Case 7 both anterior cerebral arteries were torn at the genu of the corpus callosum and death occurred 33 hours after operation. The following report was made on the microscopic studies of the left frontal lobe by Dr. Rich (the right frontal lobe had been removed in large part). The inferior portion of the left frontal lobe escaped infarction proximal to the ligation of the anterior cerebral artery except at the margins of the resected area (fig. 2, key sketch) where there was operative trauma. At the posterior margin of the operative site there was inflammation, haemorrhage, oedema and necrotic cells. A section 1 cm. posteriorly and 3 cm. in front of the Rolandic fissure showed a relatively large amount of well preserved brain surrounding foci of necrosis. Blocks made approximately 1.5 to 2 cm. in front of and behind the central fissure in the motor and sensory areas showed perfectly normal brain like the control sections.

In Case 6, in which only the gross specimen was examined, there was extensive necrosis of the mesial portions of both frontal lobes and of the white matter through the lobes and of the corpus callosum after 15 days (fig. 1), but the greater part of the frontal lobes was surprisingly firm. Unfortunately, there is no microscopic study and a subsequent more careful review of the gross defects is not possible.

In each of the three cases there is a striking difference between the immediate and complete necrosis induced in the corpus striatum by occlusion of the medial striate arteries and the partial and delayed necrosis in the remaining distribution of the anterior cerebral arteries.

The only conclusion can be that there is extensive collateral circulation between the middle and anterior cerebral arteries in the meninges over the cortex and no collateral in the vessels supplying the corpus striatum.

SUMMARY AND CONCLUSIONS

Ten cases are presented in which consciousness was immediately, almost totally and probably permanently lost after the following operative procedures: (1) resection of a frontal lobe (7 cases); (2) removal of tumors from the third ventricle (2 cases); and (3) ligation of both anterior cerebral arteries at the internal carotids (1 case). In four (4) of these cases the loss of consciousness lasted 15, 17, 23 and 51 days (until death) and is assumed to have been permanent.

In all of the 7 frontal resections both anterior cerebral arteries were sacrificed at the genu of the corpus callosum. In only two (Cases 6 and 7) of these brains have the basal ganglia been carefully studied (one microscopically). One of these showed direct trauma to the corpus striatum (right side) and the other showed necrosis of the same region (right side) from retrograde thrombosis of the anterior cerebral artery from the genu of the corpus callosum to the internal carotid artery, thus including the recurrent medial striate artery (Heubner) which supplies the anterior part of the corpus striatum. Until our attention was attracted to the basal ganglia we had been content to believe that bilateral ligations of the anterior cerebral arteries at the genu of the corpus callosum was adequate explanation for the loss of consciousness and had not carefully inspected the basal ganglia or the arterial supply. The brains have since been thrown away. We now know from other bilateral ligations of the anterior cerebral arteries at this point that deprivation of the blood supply of these vessels beyond the genu of the corpus callosum does not, per se, cause loss of consciousness.

In another case (10) both anterior cerebral arteries were ligated (clipped) at their origin from the internal carotid arteries and bilateral necrosis in the anterior portion of the corpora striata resulted and this, I think, is responsible for the loss of consciousness.

In each of the three carefully studied cases there was necrosis of the anterior part of the corpus striatum—one directly traumatic, the other two from deprivation of the blood supply. In none of the three specimens was the thalamus involved in the necrosis (two of these were microscopically studied).

In two of the 10 reported cases, the same loss of consciousness followed removal of tumors from the third ventricle and without injury of either anterior cerebral artery. These cases merely indicate that the center for consciousness is located somewhere in the basal ganglia or thalamus, but do not indicate the precise location. It is clear that in the 7 frontal lobectomies the injured part of the basal ganglia or of its blood supply must lie in the path of the resection and this could ony be in the anterior part of the corpus striatum. The optic thalamus is posterior to this line of section and therefore not involved in the trauma.

The anterior part of the hypothalamus is also beyond the line of section of the frontal lobes and for that reason could not be involved.

In two of the three cases carefully examined, the lesion in the corpus striatum was strictly unilateral and on the right side; in the third it was bilateral. It is difficult to believe that a lesion of the left corpus striatum would not act similarly but our evidence does not cover this possibility.

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STUDIES ON ALTITUDE TOLERANCE

1. Studies on Normal Rats—Effect of Repeated Short Exposures to Reduced Atmospheric Pressure[1]

G. W. THORN, M. CLINTON, JR., S. FARBER, AND H. W. EDMONDS

From the Departments of Medicine and Pathology, Harvard Medical School, the Medical Clinic of the Peter Bent Brigham Hospital, and the Department of Pathology, Children's Hospital, Boston, Massachusetts

In earlier experiments it appeared that considerable improvement in altitude tolerance could be obtained in normal animals by treatment with either small doses of cobalt (1) or large doses of adrenal cortical extract (2). Improvement in altitude tolerance of animals treated with cobalt was invariably associated with the development of polycythemia and increased hemoglobin content of the blood (3). No changes were noted in the adrenal glands of the cobalt-treated animals. Improvement in altitude tolerance of animals treated with adrenal cortical hormone in oil was not accompanied by an increase in the number of red blood cells or the hemoglobin content of the blood. The mechanism by which an excess of adrenal cortical hormone improved altitude tolerance is not known.

A limitation in the use of cobalt in the aforementioned experiments was the relatively small difference between the dose of cobalt which induced improvement and that which was definitely toxic for normal animals. Limiting factors in the use of adrenal cortical hormone for purposes of improving altitude tolerance were (a) the small quantity of material available for experimental use, (b) the high cost of preparation, and (c) the necessity of multiple subcutaneous or intramuscular injections. Since earlier experiments (4, 5) had indicated that daily exposures for short periods of time to reduced barometric

[1]The work described in this paper was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Harvard University.

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pressure in a decompression chamber resulted in both polycythemia and adrenal gland hypertrophy, it appeared worth while to investigate what effect such exposures might have on the tolerance of normal animals to "high altitude." The idea of attempting to improve performance at "high altitude" by repeated short exposures at moderate altitudes seemed to merit further study.

METHODS

Young male white rats (Sprague-Dawley strain) of approximately 200 gm. average weight were employed throughout this study. The rats were maintained on a standard diet of Purina dog chow in wire mesh cages containing ten rats per cage. Access to food and water was unrestricted at all times. The "conditioned" groups of animals were exposed to reduced barometric pressure in a large decompression chamber for a short period daily throughout the conditioning period. The rate of air flow through the chamber was in excess of 230 cubic feet of air (STP) at all altitudes. The carbon dioxide content of the chamber was at all times less than 0.5 per cent. The various groups of "conditioned" animals were exposed at reduced pressures equivalent to altitudes of 12,000, 18,000, and 26,000 feet, respectively. The temperature in the chamber ranged from 18° to 20° C. All exposures were for 2 hours at the desired pressure. "Ascent" and "descent" were carried out at a rate of 3,000 feet per minute and apparently produced no injury to the animals.

A control group of animals was maintained for each "conditioned" group. The control groups were the same age as the corresponding conditioned groups and were maintained in an identical manner except for the actual exposures.

At the conclusion of the several series of daily 2-hour exposures to 12,000, 18,000, and 26,000 feet, certain animals were sacrificed for pathological study within 24 hours of the final exposure; while others were subjected to an acute "altitude survival" test (*vide infra*).

Animals to be sacrificed were anesthetized with a lethal dose of intraperitoneally injected sodium pentobarbital solution. The animals were then killed by aspirating blood from the heart as soon as a level of anesthesia sufficient to permit exposure of the heart was reached. Following exsanguination of the animals the adrenals, thymus, heart,

and kidneys were removed, weighed on a Roller-Smith torsion balance and preserved in Zenker's solution for pathological study. Complete postmortem studies were made with histological examination of the brain, skin, bones, and all important viscera of representative animals from each group.

Acute "altitude survival" test

The acute "altitude survival" test consisted of a determination of the survival rate of groups of animals during a single 2-hour exposure to a reduced barometric pressure sufficient to produce death in at least 50 per cent of the control animals. The critical "altitude" was determined by exposing small groups of control animals to various altitudes immediately prior to running the acute "altitude survival" test. It was found that reduced pressure equivalent to altitudes of 32,000, 34,000, or 36,000 feet for 2 hours gave the most satisfactory results for animals of this size. In all of the acute "altitude survival" tests control and treated groups of animals were always exposed simultaneously in order to permit a direct comparison of survival rates. All acute "altitude survival" tests were carried out under fasting conditions. The survival rates reported represent the percentage of animals alive at the conclusion of the exposure, since all but three surviving rats in more than three hundred exposed appeared quite normal soon after return to atmospheric pressure and since no delayed deaths were noted among the several groups.

Observations

The effect of repeated previous exposures (conditioning) to various altitudes on the survival rate of groups of animals subjected to the acute "altitude survival" test is summarized in Figure I. The "altitude survival" tests presented were all conducted at a pressure equivalent to an altitude of 34,000 feet. Survival among control animals was unusual at this "altitude"; whereas aniamals which had undergone a daily 2-hour exposure to 18,000 or 26,000 feet for 30 days (conditioning) survived in most instances. Animals which had undergone repeated daily exposure (conditioning) to 12,000 feet for the same period, however, failed to survive the test. Comparison of the survival rate following seven and thirty daily 2-hour exposures

to 18,000 or 26,000 feet is of interest. The survival rate following seven exposures was 20 per cent; whereas 70 and 80 per cent of the animals which had undergone thirty daily 2-hour exposures to 18,000 and 26,000 feet, respectively, survived a single 2-hour exposure to 34,000 feet. An altitude of 18,000 feet appeared to be the critical level for improvement in rats. This is a relatively low altitude when one realizes that 80 to 90 per cent of animals of this size and strain can tolerate a 2-hour exposure to 29,000 feet.

TABLE I

Mean Organ Weights and Hematocrit Values of Rats Following Daily 2-Hour Exposures to 18,000 and 26,000 Feet

	CONTROLS	30 DAILY 2-HOUR EXPOSURES TO 18,000 FEET	7 DAILY 2-HOUR EXPOSURES TO 26,000 FEET	30 DAILY 2-HOUR EXPOSURES TO 26,000 FEET
Body Weight (gm.)	212.7	226.8*	196.9*	200.2
Adrenal Weight				
mg.	29.7	32.1	32.6*	37.9*
mg./100 gm. body weight	14.0	14.2	16.5*	19.1*
Heart Weight				
mg.	670.2	741.4*	750.7*	908.4*
mg./100 gm. body weight	315.6	327.1	381.1*	459.5*
Thymus Weight				
mg.	495.0	467.2	309.9*	313.1*
mg./100 gm. body weight	233.6	208.4	115.8*	157.1*
Hematocrit (per cent)	49.4	56.2*	57.7*	75.3*
Per Cent Surviving a 2-Hour Exposure to 34,000 Feet (from Figure I)	2.0	70.0*	20.0*	80.0*

* Indicate significant differences from corresponding control value. Chance probability less than 0.05 according to Fisher's "T" Test.

The effect of the daily 2-hour exposures on the hematocrit value and organ weight is summarized in Table I. Significant differences between exposed and control animals are indicated. It is noteworthy that a daily 2-hour exposure to 26,000 feet for either 7 or 30 days resulted in a significant alteration in the weight of the adrenals, heart, and thymus, whether considered on a relative or on an absolute basis. The adrenals and heart were heavier, while the thymus had lost

weight. Animals subjected to a daily 2-hour exposure to 18,000 feet for 30 days failed to show any significant difference in adrenal or thymus weight from unexposed control animals and showed a statistically significant increase in heart weight on an absolute but not on a relative basis. Significance was established by means of Fisher's "T" Test. Differences with a chance probability of less than 0.05 were considered significant, although most of the significant differences possessed chance probabilities of less than 0.01. The hematocrits of the exposed groups of animals were significantly elevated. It is interesting to note the dissociation between hematocrit value and survival rate (Figure II). Animals which underwent seven exposures to 26,000 feet possessed hematocrit values practically identical to those encountered in animals which underwent thirty exposures to 18,000 feet; yet the survival rates of these two groups differed markedly. On the other hand, animals which underwent thirty exposures to 18,000 or to 26,000 feet had approximately the same survival rate following a single 2-hour exposure to 34,000 feet but had a marked difference in hematocrit value (Figure II).

Microscopic examination of the tissues of rats which had undergone thirty daily 2-hour conditioning exposures at 18,000 and 26,000 feet revealed only moderate differences from the control animals. The adrenals of these animals showed partial depletion of lipoid in certain normally lipoid-rich zones when the animals were sacrificed immediately following their last exposure but exhibited no significant histological variation from the normal provided several hours elapsed between the final exposure and the sacrificing of the animal.

Animals exposed repeatedly at 18,000 feet revealed no other significant findings attributable to the experiment except for minor changes in the thymus. This organ appeared to develop larger and more prominent hemorrhages than in the controls.

Animals exposed for 2 hours each day for 30 days at 26,000 feet showed similar but less marked hemorrhages in the thymic parenchyma. These animals also had characteristic renal and cardiac lesions, however, which were absent in the control animals or in the group conditioned at 18,000 feet. The renal lesion (Figure III) consisted of inclusions of basophilic amorphous or laminated material, consistent with calcium deposits, lying between collecting tubules at the corticomedullary junction. These inclusions or incrustations

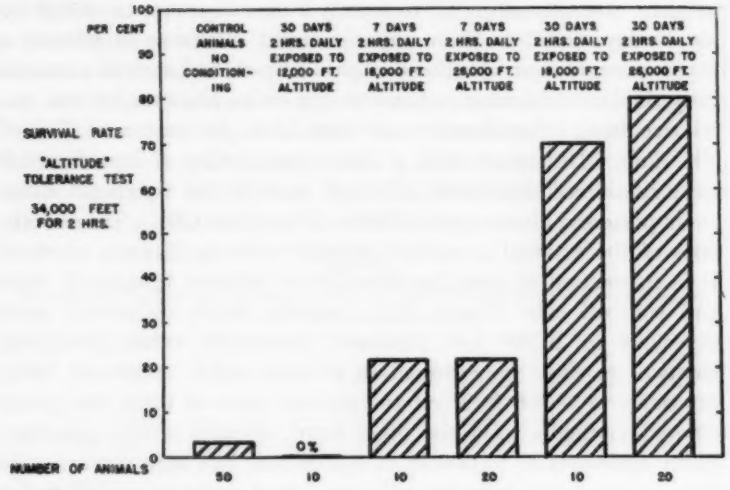


FIG. I. EFFECT OF CONDITIONING ON "ALTITUDE" TOLERANCE OF NORMAL RATS

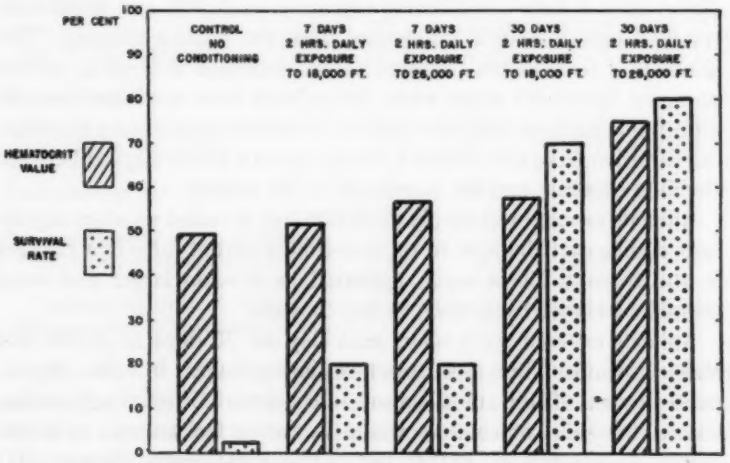
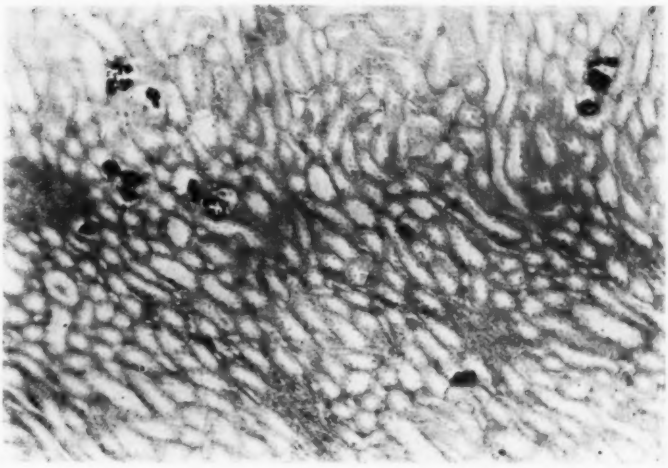
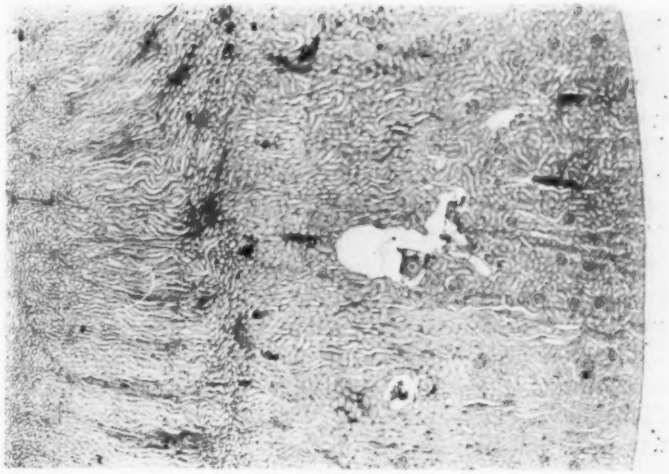


FIG. II. DISSOCIATION BETWEEN HEMATOCRIT INCREASE AND SURVIVAL RATE OF CONDITIONED RATS DURING ACUTE "ALTITUDE" SURVIVAL TEST



"High Power"



"Low Power"

FIG. III. KIDNEY—INTERSTITIAL DEPOSITS OF CALCIUM AT CORTICOMEDULLARY JUNCTION (VON KOSSA STAIN)

ranged from one to fifteen per section, and each was somewhat smaller than a glomerulus. Some of the kidneys so affected also included small groups of collecting tubules in the outer medulla which contained pale-staining hyaline casts. The capillaries adjoining these tubules were prominently congested. There were similar hyaline casts in a few of the convoluted tubules in the outer cortex in many of the kidneys. Two kidneys of the series showed localized interstitial infiltrations of lymphocytes and monocytes in between collecting tubules of the upper medulla.

The hearts in many animals which had undergone repeated conditioning exposures at 26,000 feet showed small focal cell infiltrations in the myocardium. These infiltrations were subendothelial in each instance and were not distributed at random through the myocardium.

DISCUSSION

It has been shown that animals exposed repeatedly for a short period each day to moderate altitudes are generally able to withstand a similar exposure to an extreme altitude at which normal, unconditioned animals fail to survive. The exact reason for the improved performance of the conditioned animals is not evident, but several interesting relationships were noted.

The number of conditioning exposures exerted a greater effect on survival rate during the acute "altitude survival" test than the altitude at which conditioning was carried out, provided the altitude used for conditioning was sufficient to produce any effect (Figure I).

It is not possible to relate the improvement in survival rate during the acute "altitude survival" test to alterations in organ weight or morphology, since practically no morphological changes were noted, and no significant organ weight changes were noted following repeated conditioning exposures at 18,000 feet, yet practically equal improvement was noted following exposure at 18,000 and 26,000 feet.

The improvement in performance may be related to the increased hematocrit value, but this certainly is not the only benefit derived from conditioning, since there is marked dissociation between the increase in hematocrit value and the improved survival rate. Seven daily conditioning exposures to 26,000 feet and thirty exposures to

18,000 feet resulted in practically the same increase in hematocrit value, but there was a marked difference in the survival rate of these two groups during the acute "altitude survival" test. On the other hand, animals which underwent seven conditioning exposures at 18,000 or 26,000 feet had the same survival rate, as did animals which underwent thirty such exposures at 18,000 or 26,000 feet; yet the hematocrit values of the groups of animals with similar survival rates differed widely. This dissociation in hematocrit value and survival rate is illustrated in Figure II.

It is quite probable that the improvement in survival rate at extreme altitudes is related to factors such as alterations in cellular metabolism induced by exposure to decreased oxygen pressure, since increased survival rates were not directly related to hematocrit changes and occurred in the absence of any alteration in organ weight or morphology. A study of these alterations is beyond the scope of this work. Nevertheless, it is significant that an appreciable improvement in the survival rate of animals exposed to extreme altitudes could be obtained following daily 2-hour conditioning exposures to relatively moderate altitudes. If similar improvement in altitude tolerance could be obtained in man with repeated exposures at moderate altitudes for a short period of time, it might be helpful in acclimatizing partially an individual who was changing from a life at sea level to one at a higher altitude, 10,000 to 15,000 feet (6). Such conditioning might also be helpful in rehabilitating aviators, since ability to withstand short periods of exposure to moderate "altitudes" within a decompression chamber might prove to be a useful clinical test of physical ability to return to full-time duty. The use of pressurized airplane cabins and the use of oxygen routinely at altitudes above 10,000 feet would make the practical application of such a procedure questionable in this peaceful era, but such conditions might be of value at some future date as a means of adding a slight increment to the altitudes otherwise obtainable.

Another incidental but interesting finding noted during this study was the occurrence of calcium deposits in the kidneys of animals which had undergone a daily 2-hour exposure to 26,000 feet for 30 days. These lesions were postulated as being the result of alkalosis

accompanying the blowing off of carbon dioxide due to hyperventilation stimulated by the anoxia encountered at this altitude. It is of interest that similar lesions have been encountered in the kidneys of children manifesting hyperpnea from various causes (7). Such renal damage might occur among aviators subjected to repeated bouts of anoxia and consequent hyperventilation during flights at high altitudes.

CONCLUSIONS

1. Repeated daily 2-hour conditioning exposures to 18,000 and 26,000 feet resulted in a significant increase in the survival rate of rats exposed to an altitude of 34,000 feet for 2 hours.

2. The increase in survival rate was more nearly related to the number of conditioning exposures than to the conditioning altitude.

3. Significant improvement in survival rate occurred under conditions which produced no significant alteration in organ weights or morphology.

4. There was no absolute relation between the increased survival rate at 34,000 feet and the change in hematocrit value. The improvement appeared to be due to other factors in addition to polycythemia.

5. Rats exposed to 26,000 feet for 2 hours each day developed renal lesions characterized by the collection of calciferous material in the collecting tubules. The possible significance of these lesions is considered.

ACKNOWLEDGMENT

The authors are indebted to Mr. John Carabitses for valuable technical assistance.

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STUDIES ON ALTITUDE TOLERANCE[1]

2. Studies on Normal Human Subjects—Effect of Repeated Short Exposures to Reduced Atmospheric Pressure

MARSHALL CLINTON, JR., GEORGE W. THORN AND VIRGINIA D. DAVENPORT

From the Department of Medicine, Harvard Medical School, and the Medical Clinic of the Peter Bent Brigham Hospital, Boston, Massachusetts

INTRODUCTION

Earlier experiments (1) indicated that repeated exposure of rats to reduced atmospheric pressure (27,000 feet altitude equivalent) for 3 to 6 hours daily over a period of 3 to 4 weeks was associated with a striking increase in the weight of the adrenal glands. Adrenalectomy decreased the ability of rats and dogs to survive repeated exposures to reduced atmospheric pressure (1). These facts suggested the possibility that supplementary injections of adrenal cortical hormone might be used to increase the "altitude tolerance" of normal animals. Subsequent experiments indicated that treatment with whole adrenal cortical extract was followed by a significant improvement in the performance of normal animals; whereas desoxycorticosterone acetate administration did not improve "altitude tolerance" (2).

For purposes of comparison it appeared desirable to determine what effect repeated, short, daily exposures to reduced atmospheric pressure might have on the "altitude tolerance" of normal animals. The improvement in altitude tolerance which occurs with prolonged, *continuous* residence at high altitude is of course well known (3).

It was of interest to note, therefore, that a striking increase in "altitude tolerance" was observed in normal rats exposed for 4 hours daily for 4 weeks to reduced atmospheric pressure equivalent to 27,000 feet altitude. This improvement greatly exceeded that which was observed in normal animals treated with large quantities of adrenal

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the President and Fellows of Harvard College.

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cortical hormone parenterally. Furthermore, subsequent experiments indicated that a considerable improvement in "altitude tolerance" could also be obtained by exposing normal rats for 4 hours daily for 2 to 4 weeks at reduced atmospheric pressure equivalent to only 18,000 feet altitude. These latter studies suggested the feasibility of attempting a similar type of experiment on normal human subjects in the hope that appreciable improvement in "altitude tolerance" might be gained by such a training procedure.

Since the rat is known to be more resistant than man to the effects of reduced barometric pressure, it was thought that daily exposure of human subjects for 3 hours at reduced pressure equivalent to 12,000 feet altitude might be adequate to improve "altitude tolerance." At least it seemed desirable at first to explore the possible effect of daily exposures at this "altitude" since it was known from other experiments that normal, young human subjects could be exposed safely to reduced pressure equivalent to this altitude.

PLAN OF STUDY

Since so little is known (4) concerning the metabolic changes which might be expected to occur in human subjects following daily exposure for 3 hours at reduced atmospheric pressure equivalent to 12,000 feet, and since any marked change in general physical condition might be expected to affect "altitude tolerance," it was considered advisable to follow closely the metabolic changes which might occur in normal subjects during the experiment. For this reason four of the subjects in this experiment lived on the Metabolic Ward of the Peter Bent Brigham Hospital and were fed a diet of constant composition throughout the experiment; fluid intake was also kept constant. Twenty-four-hour urine collections, and 72-hour stool collections were made. The activities of a second group of normal subjects (medical students) were unrestricted, except for the 3-hour period of exposure in the decompression chamber each evening following dinner and the overnight stay in the hospital once weekly prior to the "altitude tolerance" test. A third group of medical students acted as controls. These latter normal subjects were given all of the tests administered to the first and second groups of subjects, including the weekly "altitude tolerance" test, but they were not exposed in the decompression chamber.

METHODS

The subjects undergoing these experiments were young males 21 to 32 years of age, all of whom had been subjected to a careful medical examination, including electrocardiogram, chest x-ray, hemoglobin determination and urinalysis, and had been found to be free of ogranic disease. All but two of the subjects were exposed to reduced atmospheric pressure for 3 hours daily. The decompression chamber measured 29′1″ (length) x 6′6″ (height) x 8′ (width) and was divided into two compartments connected by a small anteroom. The chamber was large enough to allow the occupants to sit, stand, walk about, or lie down. During the period of exposure (3 hours) they were able to read, study, and listen to the radio. At the reduction in atmospheric pressure (12,000 feet altitude equivalent) employed in these experiments the ventilation rate through the chamber was 600 cubic feet per minute. During the 3-hour exposure periods the temperature in the chamber was maintained at 20° C. ±1° Decompression was accomplished within 3 to 4 minutes, at a rate equivalent to 3,000 to 4,000 feet of altitude per minute. Recompression was carried out more slowly, usually at a rate equivalent to 1,500 to 2,000 feet of altitude per minute. All subjects exposed to reduced atmospheric pressure were given "altitude tolerance" tests prior to the exposure period, at appropriate intervals during the course of the exposure period, and at intervals for 2 to 6 weeks following the last exposure in the decompression chamber. Two subjects not exposed to reduced pressure were given "altitude tolerance" tests at intervals corresponding to those of the "treated" group.

The "altitude tolerance" test was conducted as outlined below: Following an overnight stay on the Metabolic Ward, the subject, under strictly basal conditions, was seated on a low stool and instructed to breath through a soft rubber mouth piece connected by flutter valves and tubing to a 120-liter gasometer. The valves and tubing were so arranged that the subject inspired directly from the gasometer and expired through a soda lime chamber into either the gasometer or the room (figure 1). Prior to the start of the test the gasometer was charged with approximately 55 to 60 liters of fresh air. The subject was then allowed to inspire from the gasometer and expire into the room until such time as the gasometer bell contained

exactly 50 liters of air at the end of an inspiration. At this time a valve was turned and the subject then expired into the gasometer. Ade-

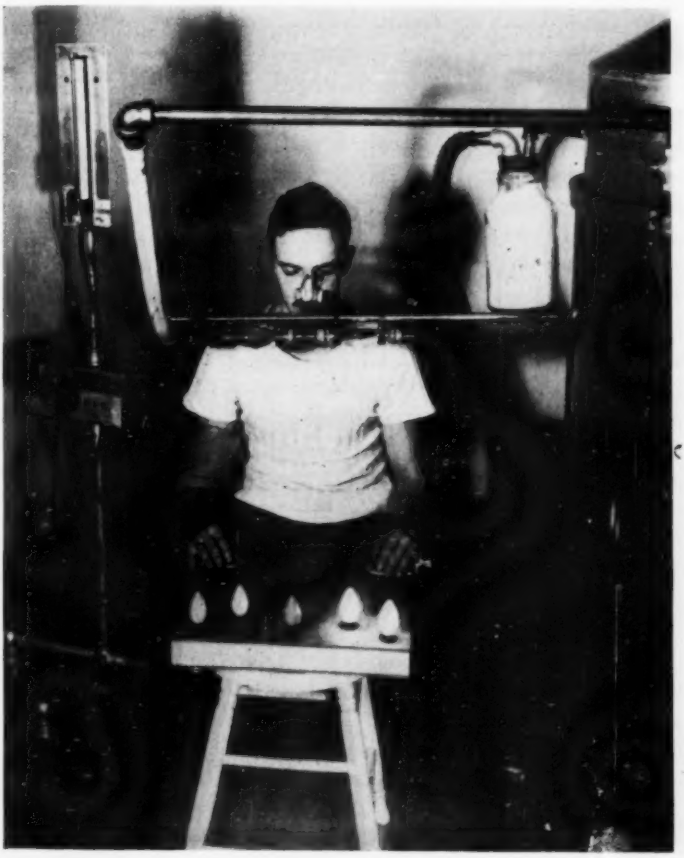

FIG. 1. REBREATHING AND SIGNAL APPARATUS FOR ACUTE "ALTITUDE TOLERANCE" TEST

quate mixing of the air within the gasometer was affected by a small electric fan contained within the gasometer bell at the mouth of the return-flow pipe. The test was timed by a stopwatch. As rebreathing

proceeded pulse and blood pressure were determined at specified intervals by one observer, while another observer determined the subject's ability to respond to light signals.

The signal device consisted of a board placed in front of the subject containing two rows of electric lights and two toggle switches (figure 1). The rear row of lights contained three small electric bulbs controlled by the observer while the front tow of lights contained two small electric bulbs each of which was controlled by the diagonally opposite toggle switch. The subject was instructed to light the corresponding bulb in the front row whenever either end bulb of the rear row was lighted by the observer and to light both front bulbs whenever the center bulb of the rear row was lighted. Testing was kept up continually throughout the experiment except for brief periods when blood pressure and pulse rate were being taken. With this apparatus it was possible to use the subject's inability to respond to light signals as an objective end point for the termination of the test. This end-point was sharp in all cases; complete inability to respond to light signals occurred following a period of less than 1 to 2 minutes of delayed or erroneous response. As soon as the subject became unable to respond to the light signals the test was stopped; the mouth piece was removed; and the subject was allowed to breath room air. In addition, he was lowered immediately into a horizontal position. Syncope was avoided by prompt termination of the test when the end-point (inability to respond to light signals) was reached. Recovery was prompt. The time between the start of rebreathing and the end-point of the test was measured carefully. On completion of the test the air remaining in the gasometer was analyzed in a Haldane gas analyzer in order to determine the per cent of oxygen (altitude) and carbon dioxide present in the gasometer.

The following modifications of the original rebreathing test as described by Schneider (5) improved the accuracy and reproducibility of the test:

1. All tests were performed under *strictly basal conditions*.
2. The volume of air used in rebreathing was 50 liters.
3. The oxygen content of the air remaining in the spirometer at the conclusion of the test was measured (modified Haldane gasometer).

4. Failure to respond to light signals was taken as the end-point rather than syncope or circulatory collapse.

Since the quantity of oxygen available during the test was constant for all subjects (50 liters of air being the volume in the spirometer available for rebreathing), the *duration of the test* varied directly with the subject's ability to withstand the effects of anoxia; and indirectly with surface area and basal metabolic rate. The per cent of oxygen attained in the spirometer at the end of the experiment (altitude) did not appear to be correlated among different subjects with surface area, basal metabolic rate, or duration of test. In these studies each subject served as his own control, since little change in surface area or basal metabolic rate was observed during the experiment. Results of the test are recorded as "final altitudes attained" (per cent oxygen in air in spirometer at time test was concluded).

The subjects exposed to reduced atmospheric pressure were divided into two groups. One group (four subjects) lived on the Metabolic Ward and were subjected to detailed metabolic study during the course of the experiment. The remaining group (eight subjects) reported for exposure each day and underwent acute "altitude tolerance" tests at intervals of approximately 1 week, but otherwise were not restricted in their activities. The subjects living on the Metabolic Ward were provided with a constant diet and a constant fluid intake. Daily urine volume was measured, and the urinary output of nitrogen, chloride, and phosphate was followed. Stool analysis for nitrogen and fat was performed on 3-day stool samples collected prior to, during, and at the end of the exposure period. Plasma volume and heart size (teleoroentgenogram) were determined prior to and at the end of the exposure periods. Seventeen-ketosteroid excretion was measured at intervals throughout the experiment. Basal metabolic rate and oxygen consumption while walking on a motor-driven treadmill were determined for each subject twice each week. At appropriate intervals blood was withdrawn from the antecubital vein with minimal stasis and analysed for hemoglobin, hematocrit value, total serum protein, serum sodium, potassium, chloride, and carbon dioxide combining power. The methods employed have been described elsewhere (6).

OBSERVATIONS

General Considerations

All of the subjects except two who were exposed for 3 hours daily in the decompression chamber at reduced atmospheric pressure equivalent to 12,000 feet altitude completed the series of exposures in excellent condition. One subject was forced to discontinue exposures temporarily because of the onset of an intercurrent upper respiratory tract infection, and one subject was noted to develop frequent premature auricular contractions of the heart during the evening of his twelfth exposure; since this irregularity in cardiac rhythm persisted through the following day, it was decided to withdraw him from the experiment (vide infra-cardiac studies).

The subjects who underwent the exposures noted no untoward symptoms. Headache, sleepiness, marked mental and physical fatigue, and disinclination for work and even for recreation which were noted in Armstrong's studies (4) on subjects exposed for 4 hours at a similar altitude equivalent were not observed in these students. Measured work performance on a motor-driven treadmill revealed, if anything, a slight increase in efficiency during the latter part of the exposure period. The remarkable increase in appetite and urine volume reported by Armstrong (4) was not observed in either the group of subjects on controlled diet and fluid intake or the group permitted food and fluid ad libitum.

1. *Effect on "Altitude Tolerance".* The changes which were observed in "altitude tolerance" during and following daily exposures in the decompression chamber are presented in Chart 1. Equivalent-altitude values were calculated directly from the oxygen content of the air in the spirometer at the termination of the "altitude tolerance" test, the end-point being taken as the time at which the subject could no longer respond to the signal lights (see Methods). Improvement in "altitude tolerance" was observed at the end of 2 or 4 weeks of daily exposures in ten of the eleven subjects (Table 1). This improvement varied from 1,000 to 7,300 feet "altitude" equivalent. Improvement in performance of the test was characterized by:

1. A lower content of oxygen in the air remaining in the spirometer at termination of the test (higher "altitude" attained).
2. An increase in the time which elapsed before the subject failed to respond to the lights (increased duration of test).

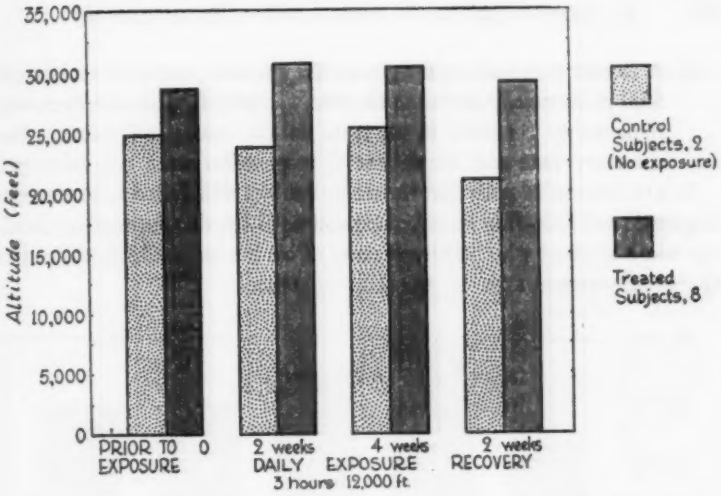

CHART 1. CHANGES IN "ALTITUDE TOLERANCE" FOLLOWING DAILY EXPOSURE TO REDUCED ATMOSPHERIC PRESSURE (12,000 FEET ALTITUDE)

TABLE 1

Changes in "Altitude Tolerance" following Daily Exposure for 3 Hours to Reduced Atmospheric Pressure Equivalent to 12,000 Feet Altitude

SUBJECT	PRIOR TO EXPOSURE	ALTITUDE EQUIVALENT (FEET)			
		Following 2 weeks of exposures	Following 4 weeks of exposures	2 weeks after last exposure	4 weeks after last exposure
Group A					
D. W. B.	29,900	31,100	30,200	31,600	29,200
H. T. B.	28,000	30,500	30,900	27,500	29,800
W. F. B.	31,100	30,600	30,700	28,000	
J. G. H.	22,200	28,000	27,400	29,000	26,900
C. J. J.	29,600	30,800	30,700	29,400	
M. J. P.	27,300	34,600	32,300	30,200	29,300
C. A. S.	30,400	30,600	31,800	28,300	29,200
J. R. W.	28,800	29,500	29,800	27,800	29,300
Group B					
L. A. B.	24,300	28,600			27,400
D. R. M.	24,600	27,200			30,500
W. R. R.	25,200	29,500			28,300
Group C (control subjects—no exposure)					
J. T. B.	27,100	23,600	27,000	27,200	23,800
L. R. B.	22,600	23,600	23,200	24,000	22,900

3. A slower pulse rate throughout the greater part of the test; the final pulse rate at the time the test was terminated, however, was remarkably constant in all tests on the same individual. Respiratory rate and amplitude of respiration were not recorded.

It is of interest to note that the single subject who failed to show some improvement following repeated exposures in the decompression chamber was a student who had lived most of his life on the high plateau in the southwestern area of the United States!

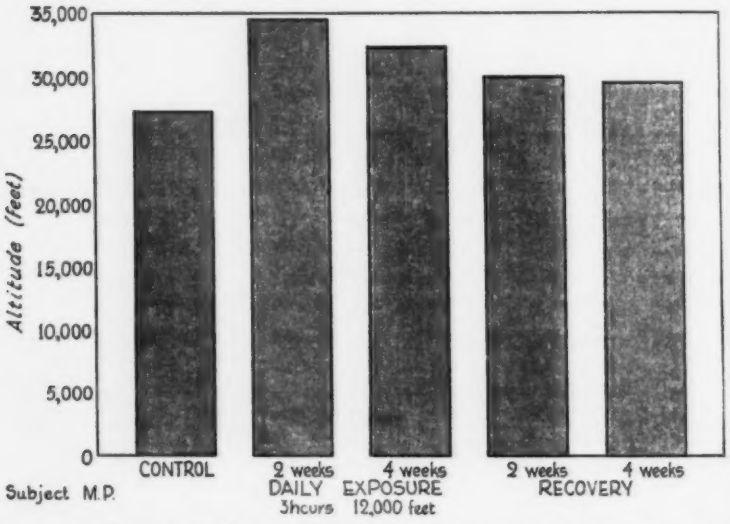

CHART 2. CHANGES IN "ALTITUDE TOLERANCE" FOLLOWING DAILY EXPOSURE TO REDUCED ATMOSPHERIC PRESSURE (12,000 FEET ALTITUDE)

Statistical analysis of the data in Table 1 revealed the fact that the difference between the mean values obtained prior to exposure and those following 2 to 4 weeks of exposure were significant (value of "P" = 0.02).

Data on one of the subjects (M. J. P.) who showed improvement in "altitude tolerance" are presented in Chart 2.

Three of the seven subjects (Group A) who improved during the 4 weeks of exposure displayed maximum improvement at the end of the

2nd week of exposures; the remaining four showed maximum improvement during the 3rd and 4th weeks of exposures.

TABLE 2

"Altitude Tolerance" Test—Typical Experiment

Normal Subject W. R. R.

TIME	PULSE RATE				
	Prior to exposure period			Following 12 daily exposures	26 days following last exposure
	Date				
	4/3/43	4/11/43	4/13/43	4/25/43	5/21/43
	Body weight (kg.)				
	77.6	77.4	77.7	76.4	77.2
minutes					
0	62	60	64	66	70
4	62	62	62	68	72
8	66	60	58	62	72
12	62	64	62	66	68
15	64	68	66	66	70
18	64	70	70	66	72
20	68	82	78	72	75
22	80	82	88	72	75
24	84	96	88	74	80
25	90	100*	96	81	84
26	96		96	80	88
27	104		104	88	94
28	108*		108*	88	100
29				90	100*
30				96	
31				96	
32				100+*	
Oxygen content of air remaining in spirometer at end of test	7.61%	7.76%	7.68%	6.36%	6.71%
Altitude equivalent	25,500	24,900	25,200	29,500	28,300

* Test stopped at this time because of subject's inability to answer light signals.

In the majority of subjects there was loss of improved "altitude tolerance" within 2 to 4 weeks following the last exposure in the decompression chamber (Table 1). Although the average value for

"altitude tolerance" was still somewhat increased when tested 4 weeks after exposures had been discontinued, analysis of these data revealed that the difference between the means (prior to exposure and 4 weeks after the last exposure) was probably not significant (value for "P" = 0.2–0.1).

Three additional subjects who were exposed for 14 days only were also observed to have an increase in "altitude tolerance" at the end of this period (Table 1, see subjects L. A. B., D. R. M., and W. R. R.). The protocol on subject W. R. R. is presented in Table 2.

Two control subjects (Table 1, Group C) who were given repeated "altitude tolerance" tests at intervals corresponding to those given the group exposed in the decompression chamber were observed to have no consistent change in "altitude tolerance" during the experiment. One of the subjects (J. T. B.) was noted to have rather marked "spontaneous" fluctuations in "altitude tolerance"; whereas the second subject (L. R. R.) had remarkably constant tests.

TABLE 3

Effect of Administration of 17-Hydroxycorticosterone (33 Mg.) on "Altitude Tolerance"

Normal Subject G. E.

PRIOR TO HORMONE THERAPY	DAY OF HORMONE THERAPY	2 DAYS FOLLOWING HORMONE THERAPY	2 WEEKS FOLLOWING HORMONE THERAPY
	"altitude tolerance" feet		
29,900	30,000	29,400	29,900

The effect of a single exposure of 3 hours at reduced atmospheric pressure equivalent to 12,000 feet altitude on the performance of the "altitude tolerance" test was investigated on several occasions. No improvement in "altitude tolerance" followed a single exposure for 3 hours at 12,000 feet altitude-equivalent.

On three occasions an opportunity presented itself to observe the effect of a slight respiratory infection on performance as measured by the "altitude tolerance" test; in all instances, despite the absence of fever and constitutional reaction in the subjects, there was an appreciable reduction in "altitude tolerance" during and immediately following the period of infection.

In one subject the effect of a rather large dose (33 mg.) of 17-hydroxycorticosterone (adrenal steroid with carbohydrate-regulating

potentiality) was studied (Table 3). No significant change in "altitude tolerance" occurred following treatment. Because of the limited quantity of this compound additional tests could not be made.

2. *Metabolic Studies. Body Weight:* A slight, but progressive weight loss (0.35 kg. per week—average) occurred in three subjects maintained on a constant diet throughout the experiment (Table 4). To some extent this loss was due to insufficient calories calculated for the basic maintenance diet, since slight weight loss was observed in these individuals on the constant diet during the control period prior to instituting the daily exposures in the decompression chamber. It is obvious, however, that the period of greatest weight loss occurred during the 3rd and 4th weeks of exposure (Table 4). Weight loss during

TABLE 4

Changes in Body Weight following Daily Exposure to Reduced Atmospheric Pressure
(12,000 feet altitude equivalent)

GROUP	BODY WEIGHT (KG.)			
	Prior to exposure	Following 2 weeks of exposures	Following 4 weeks of exposures	2–4 weeks following last exposures
3 subjects on constant diet	62.9	62.4	61.5	61.1
7 subjects on unrestricted diet	71.8	71.5	71.4	71.2

the exposure period could not be explained by impaired absorption of food or increased basal metabolic rate (vide infra).

The seven subjects on an unrestricted diet lost weight at the rate of 0.10 kg. per week (average), or a total loss of 0.60 kg. throughout the entire experiment. There was no evidence of any significant change in food habits in any of these subjects. No weight loss was noted in the two control subjects (unrestricted diet) during this same period.

Cardiac Studies: Teleoroentgenograms were made prior to beginning the exposures and at the conclusion of the 4 weeks of exposures. No significant change in cardiac size or in the electrocardiogram was observed during the experiment. One subject developed a cardiac irregularity (premature auricular contractions) which was first noted during the evening of the twelfth exposure. This irregularity in rhythm persisted throughout the following day, and although there

was no evidence of circulatory embarrassment, it was thought wise to withdraw this subject from the experiment. Subsequently, he was exposed once again for 3 hours to reduced atmospheric pressure equivalent to 12,000 feet altitude, and the irregularity in cardiac rhythm returned. It appeared, therefore, that the cardiac regulating mechanism in this individual was unusually sensitive to the effect of anoxia. The irregularity in rhythm could also be induced rather easily in this subject by continued rebreathing (20 to 25 minutes) from a spirometer

TABLE 5

Hematocrit Values and Serum Protein Concentration following Daily Exposure to Reduced Atmospheric Pressure

NUMBER OF SUBJECTS	HEMATOCRIT VALUE (PER CENT VOLUME PACKED RED BLOOD CELLS)	
	Prior to exposures	At conclusion of 4 weeks of daily exposures
8	45.8	47.3
	TOTAL SERUM PROTEIN (GM./100 CC.)	
4	7.4	6.9

TABLE 6

Changes in Blood Volume following Daily Exposure to Reduced Atmospheric Pressure

NUMBER OF SUBJECTS	PRIOR TO EXPOSURE			FOLLOWING 4 WEEKS OF DAILY EXPOSURES			
	Plasma volume	Red blood cell volume	Total blood volume	Plasma volume	Red blood cell volume	Total blood volume	Increase
	cc.	*cc.*	*cc.*	*cc.*	*cc.*	*cc.*	%
3	2860	2400	5260	2880	2500	5380	2

(50 liter content—fresh air), the carbon dioxide of the exhaled air being removed by absorption by calcium hydroxide.

Blood Studies: No significant change was observed in hematocrit values (eight subjects) and blood volume (three subjects) following 4 weeks of daily exposure for 3 hours at a simulated altitude of 12,000 feet (Tables 5 and 6). Furthermore, no significant changes in blood chemistry values occurred in the three subjects maintained on a constant metabolic regimen throughout the experiment (Table 7).

Urinary Excretion: Nitrogen excretion decreased appreciably during the period of exposure in the decompression chamber (Chart 3).

TABLE 7

Changes in Blood Chemistry Values following Daily Exposure to Reduced Atmospheric Pressure

	CONTROL	CONTROL 1 WEEK LATER	FOLLOWING 2 WEEKS OF EXPOSURES	FOLLOWING 4 WEEKS OF EXPOSURES
Blood nonprotein nitrogen (mg./100 cc.)	30	28	31	28
Serum sodium (m.eq./liter)		147	145	144
Serum chloride (m.eq./liter)	103	102	107	108
Serum carbon dioxide combining power (m.mol./liter)		27.1	28.4	29.5
Total serum protein (gm./100 cc.)	7.3	7.0	6.7	6.8
Serum albumin (gm./100 cc.)	4.5			3.8
Serum globulin (gm./100 cc.)	2.8			3.0
Blood sugar (mg./100 cc.)		75	76	

Average values for 3 normal subjects on constant diet and constant fluid intake.

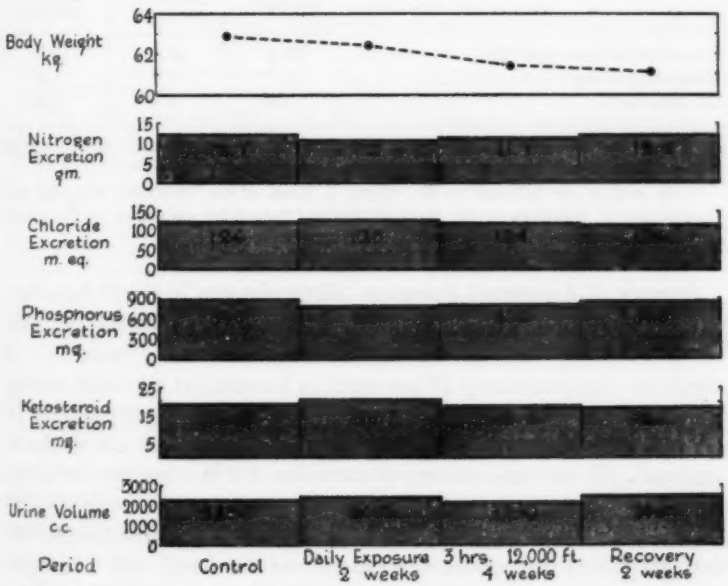

CHART 3. METABOLIC CHANGES FOLLOWING DAILY EXPOSURE TO REDUCED ATMOSPHERIC PRESSURE (12,000 FEET ALTITUDE)
Mean of subjects J. G. H., D. W. B. and M. J. P

Changes in phosphorus excretion paralleled those of nitrogen. No significant changes in urine volume or chloride excretion were observed in the three subjects maintained on constant diet and fluid intake.

Fecal Analyses: No significant change in the character or volume of the stools was observed during the experiment. Analysis of the stool for nitrogen and fat revealed ***no significant*** changes (Table 8). The increased loss in weight which occurred throughout the 4 weeks' exposure period could not be attributed, therefore, to impaired absorption of food, and the decrease in urinary nitrogen excretion during this period represented a positive nitrogen balance.

TABLE 8

Studies of Fecal Nitrogen and Fat Excretion following Daily Exposure to Reduced Atmospheric Pressure[*]

	PRIOR TO EXPOSURE	FOLLOWING 2 WEEKS OF EXPOSURES	FOLLOWING 4 WEEKS OF EXPOSURES
Dry weight of feces (gm./day)	20.9	20.1	17.1
Nitrogen (gm./day)	1.3	1.3	1.2
Fat (gm./day)	3.0	2.4	2.9

Average for 3 subjects maintained on constant diet and fluid intake; diet contained 13.7 gm. nitrogen and 97.2 gm. fat, daily.

[*] The authors are indebted to Dr. Alfred T. Shohl of the Children's Hospital and Department of Pediatrics of the Harvard Medical School for assistance in the above analyses.

Urinary 17-Ketosteroid Excretion: Slight changes in the 17-ketosteroid excretion were observed in the three subjects maintained on a constant metabolic regimen throughout the experiment (Table 9). A slight rise (approximately 10 per cent) in ketosteroid excretion during the first 2 weeks of exposure was followed by a fall (approximately 10 per cent) below initial control values during the 3rd and 4th weeks of exposure. Seventeen-ketosteroid excretion did not return to initial control level during the 2 weeks' recovery period. It is possible that these slight changes may have some significance; it is evident, however, that all values throughout the experiment were well within normal range for young healthy, male subjects (7).

Basal Metabolic Rate: Determinations of basal metabolic rate were made in the three subjects on constant metabolic regimen (Table 10).

A slight decrease (average 4 to 5 per cent) in basal metabolic rate was observed as the experiment progressed. During the recovery period, however, the rate did not return to the initial control level. It is probable that the slight progressive decrease in basal metabolic rate was merely an accompaniment of weight loss, since the inclination for metabolic rate to fall with loss in weight due to insufficient caloric intake is well known.

TABLE 9

*Changes in 17-Ketosteroid Excretion following Daily Exposure to Reduced Atmospheric Pressure**

NUMBER OF SUBJECTS	17-KETOSTEROID EXCRETION (MG./24 HOURS)			
	Prior to exposures	Following 1–2 weeks of exposures	Following 3–4 weeks of exposures	2 weeks following last exposure
3	19.9	20.7	18.6	18.1
	URINE VOLUME (CC./24 HOURS)			
3	2350.0	2410.0	2250.0	2460.0

Average for three subjects on constant metabolic regimen.

* The authors are indebted to Dr. Harry B. Friedgood of the Peter Bent Brigham Hospital and Department of Medicine of the Harvard Medical School for the urinary 17-ketosteroid analyses.

TABLE 10

Changes in Basal Metabolic Rate following Exposure to Reduced Atmospheric Pressure

NUMBER OF SUBJECTS	BASAL METABOLIC RATE (PER CENT OF STANDARD)			
	Prior to exposure	Following 2 weeks of exposures	Following 4 weeks of exposures	2 weeks following last exposure
3	−2	−6	−7	−6

Average for 3 subjects maintained on constant metabolic regimen.

Vital Capacity: No significant change in vital capacity occurred during the 4 weeks of exposure in any of the subjects. Prior to exposure the average vital capacity was 4.8 liters; at the end of 4 weeks of exposure, 4.9 liters; and during the recovery period, 4.8 liters.

Work Performance on Treadmill: As a measure of physical condition, the three subjects on constant metabolic regimen walked daily on a motor-driven treadmill for a period of 10 minutes, at a rate of 4 miles

per hour for subjects (J. G. H. and D. W. B.) and 3.5 miles per hour for subject (M. J. P.) on an 8.6 per cent grade. Oxygen consumption in performing this amount of work gradually decreased throughout the experiment. The average value prior to exposure was 18.7 liters of oxygen per 10 minute unit period; at the end of 2 weeks of exposure the oxygen consumption was 18.4 liters; at the end of 4 weeks of exposure 17.8 liters of oxygen, and during the recovery period, 17.5 liters of oxygen per 10 minute unit period.

It is unlikely that training was responsible for the improvement, since the men were exercised daily for several days prior to the beginning of the exposures and since no change was observed in the oxygen consumption of subject G. E., control subject during the same period.

Electro-encephalogram: In three subjects electro-encephalograms made prior to exposure and again following 4 weeks of exposure revealed no significant difference in any of the subjects.

DISCUSSION

It is obvious that the "altitude tolerance" test employed in this experiment did not simulate the exact conditions encountered in high altitude flying; however, the test had the advantage that it could be given repeatedly without ill effect to the subject. A test which measures maximum performance will obviously be affected significantly by changes in the subject's physical condition such as fatigue, the presence of respiratory infections, etc. To improve reproducibility of performance great care was employed in standardizing the conditions surrounding the test; hence the subjects were admitted to the hospital ward on the evening preceding the test and the test was performed on the following morning under strictly basal conditions. Such a technique improved reproducibility of performance but also definitely limited the number of subjects who could be investigated. Although repeated control tests were desirable, it was anticipated that repeated testing might in itself improve or significantly affect "altitude tolerance." To determine this control subjects were tested repeatedly for the effect of such testing on "altitude tolerance." Unfortunately definite conclusions could not be drawn from these experiments because certain subjects appeared to be very constant on repeated testing and showed no significant improvement as the result

of testing; whereas other subjects showed considerable improvement during the first few tests and then attained a plateau which was maintained.

Armstrong (4) reported that symptoms of "chronic anoxia" appeared in both groups of his subjects, i.e. those exposed for 4 hours and those exposed for 7 hours daily, 6 days a week at a reduced atmospheric pressure equivalent to 12,000 feet. He did not specify the temperature in the chamber or state whether a constant temperature was maintained throughout the experiment. He did note that the symtoms experienced by the 7 hour group were not markedly different from those experienced by the 4-hour group. In our experiment the men were exposed for 3 hours daily 7 days a week for 4 weeks; the temperature in the chamber was maintained at 20°C. No untoward symptoms were observed in this group of subjects.

Armstrong noted an increase in appetite (50 to 100 per cent) and an increase in urine volume, although he states no constant dietary regimen was provided or accurate measurement of food and fluid intake made. In the present study, subjects on food and fluid ad libitum experienced no measurable change in food and fluid intake and in urine output. Weight change was minimal; i.e. a loss of 0.1 kg. per week. Three subjects were followed very carefully on a constant diet and fluid intake; no significant changes were observed in fluid balance; weight loss amounted to 0.3 kg. (average) per subject per week during the exposures. Part of this weight loss was due to slight insufficiency of caloric content of the control diet, since a slight weight loss was noted during the preliminary control period on this diet prior to beginning the daily exposures in the decompression chamber. Since the greatest rate of weight loss, however, occurred during the 3rd and 4th weeks of exposures, and since the rate of weight loss decreased somewhat during the subsequent control period, it is fair to assume that a slight increase in caloric requirement occurred in these subjects during the period of exposures in the decompression chamber. This change was not due to a rise in basal metabolic rate and was not due to failure to absorb protein and fat. An increased retention of nitrogen and phosphorus occurred during the period of exposures.

Studies relating to adrenal cortical function during these exper-

iments revealed little. No significant change in sodium or chloride balance was observed throughout the experiment. Seventeen-ketosteroid excretion fluctuated slightly but insignificantly; the administration of a relatively large single dose of 17-hydroxycorticosterone did not affect the "altitude tolerance" test (one subject).

It is our belief that daily exposures to reduced pressure equivalent to 12,000 feet are relatively safe and feasible. Daily exposures, for at least 4 weeks, are well tolerated by young, healthy male subjects. Metabolic studies reveal no deleterious or significant change from normal. It appears unlikely that such exposures would affect significantly the "ceiling" of aviators who are flying regularly at high altitudes, 30,000 feet or more, with supplementary oxygen, where mild degrees of anoxia must be experienced. However, in the rehabilitation of aviators who have been grounded (illness, accident, etc.) such a course of preliminary exposures might be extremely beneficial (a) in improving the individual's tolerance and (b) as an indication of whether the aviator was physically able to resume flying. The construction of decompression chambers for use at these relatively small reductions in atmospheric pressure would be quite feasible. Since men can read, play cards and games, etc. during the 3-hour period, the exposures could be used as periods of "relaxation"; with an adequate "lock" arrangement men could come and go throughout the day and a relatively small chamber could thus be used to condition a large number of men. Since animal experiments indicate so clearly that great improvement in altitude tolerance can be gained by short repeated daily exposures, it would appear worth while to give this technique serious consideration.

CONCLUSIONS

1. Preliminary studies indicated that 3-hour daily exposures for a period of 4 weeks at a reduced pressure equivalent to 12,000 feet altitude were well tolerated by normal, healthy young male subjects. No evidence of chronic altitude sickness was observed in any of the subjects.

2. A modification of the Schneider rebreathing test was employed to measure changes in "altitude tolerance" following repeated exposures in the decompression chamber.

3. Improvement in "altitude tolerance" was observed in ten of eleven

subjects during the 2nd to 4th week of daily exposures. Improvement was not accompanied by an increase in red blood cell count, hemoglobin value, or cardiac size.

4. Metabolic studies indicated that no significant change occurred in appetite, gastro-intestinal absorption, urine volume, or renal excretion of chloride during the period of exposures. Nitrogen and phosphorus were retained during the period of exposures.

5. Studies relating to adrenal cortical function revealed little. No significant change in sodium or chloride balance occurred as the result of repeated daily exposures to decreased atmospheric pressure; 17-ketosteroid excretion fluctuated slightly but insignificantly. The administration of a relatively large single dose of 17-hydroxycorticosterone did not affect the "altitude toleranee" test (one subject).

ACKNOWLEDGMENTS

The authors are indebted to Miss Marion J. Brian, dietician, Miss Janet E. Clark, nurse in charge of the metabolic studies, and to Mrs. Grete Heinemann, technician, for their continued cooperation throughout this study. The authors also wish to express their appreciation to Dr. Cecil K. Drinker and to Mr. Robert M. Thompson of the School of Public Health, Harvard University, for their assistance and valuable suggestions.

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PROCEEDINGS OF THE MEETINGS OF THE JOHNS HOPKINS MEDICAL SOCIETY.

Held in Hurd Memorial Hall, November 12, 1945.

Diagnostic Methods in Chronic Brucellosis. EARL L. BURKEY (*Department of Ophthamology*).

Several recent developments in the diagnosis and treatment of brucellosis in man and animals were described. These will be reported in more detail in a later number of this journal.

DISCUSSION

Dr. Perrin H. Long: I would like to comment on Dr. Burky's paper. In individuals returning from the Mediterranean or North African theatres who have a history of prolonged fever of unknown origin, one must always suspect brucellosis. Despite many directives regarding the contamination and undesirability of native food, there were cases of brucellosis especially in Sicily or Italy, in soldiers who drank raw milk or ate native cheese. I remember one very striking incident which occurred during the period when we were hemmed in on the Anzio beachhead. A platoon of the First Special Service Force caught a cow. They did not have a veterinarian to approve it so they asked a dental officer to inspect it. He said that the cow "looks all right to me". These boys had not had fresh milk for the many months which they had been away from the States, and to have a nice cow which gave good warm milk—because it was very cold—seemed to them to be a very fine thing. The difficulty was that 19 cases of brucellosis developed in this platoon, and there were other individuals in it who had prolonged fever of unknown origin which was suspected to be brucellosis but which was not proved beyond doubt. So it is very important in individuals coming from other parts of the world (especially our part of the world because I know the sanitary directives were not observed), if they give a suggestive history to suspect brucellosis, since there was probably far more brucellosis than was recognized because, as Dr. Burky points out, the diagnostic procedures are several, and we had available only the agglutination test, and many times with that test, I am quite sure, the antigen used was not very reliable.

Colonel John T. King: In most of the patients we saw at Walter Reed, the suspected infections were not acquired in line of duty. The patients had gone on a holiday in the country or had acquired the infection before coming into the service. Pecularly enough, among nurses and WACs, the suspected cases ran higher than among soldiers and officers; why I do not know. The whole question of diagnosis, as you doubtless all realize, is very difficult. I do not know any more unsatisfactory state of affairs than making a flat-footed diagnosis of brucellosis.

Something such as Dr. Burky is describing tonight in making a diagnosis is going to be very helpful to everyone.

Dr. Burky: Dr. Wolman has just whispered in my ear whether there is anything new in treatment. A veterinarian friend of mine, in talking over the treatment of animals, told me that this fistulous wither, once the abscess opens, drains indefinitely. One injection and sometimes two of strain 19 will heal them. On the basis of that, the veterinarians are injecting themselves with strain 19 and expect to be able to announce very shortly that it is a useful method.

Combat Exhaustion. JOHN C. WHITEHORN (*Department of Psychiatry*).

A five man psychiatric mission (of which the author was a member) made a clinical study of "combat exhaustion" in the European Theatre of Operations in the Spring of 1945, for OSRD and the Army. Observations were made in the 9th, 1st, 3rd and 7th Armies in Germany. Victory was in prospect, the front was very mobile and the psychiatric casualty rate was relatively low, but the commission had opportunities to study acute conditions from the hotly-contested region near Leipzig. Progressively more chronic sequelae were studied in other rest centers and hospitals, and the experiences and opinions of many physicians were compared. V-E Day came when the mission was in Czechoslovakia.

The acute psychiatric disabilities occurring in combat should be distinguished from normal states of extreme anxiety and tension which also occur in combat but do not disable the soldier. Promptness and good judgement in making this distinction, and in providing appropriate psychiatric first aid treatment had been developed to a point of considerable effectiveness, so that a very large proportion of such casualties were being salvaged. In the total ETO operation, 90% of the psychiatric casualties were returned to duty, about half of them to combat duty. Probably the most important single factor in this success was the divisional psychiatrist. The Army neurosis centers also did effective work. Special psychiatric hospitals in the zone of communications, receiving those who had not responded promptly, restored many to non-combat effectiveness and a few to combat. Psychiatric sections in general hospitals did not have quite such good success. In early beach-head operations, where the tactical situation necessitated immediate evacuation to a distant base, only 3 to 5% were returned to duty. Without prompt treatment, there was a marked tendency toward the development of typical neurotic fixation of symptoms.

Spectacularly good recoveries sometimes were made. Men who were returned to combat by competent and experienced psychiatrists had records of good service not markedly different from controls, but the records are confused by the fact that psychiatric recommendations against reassignment to combat duty were sometimes disregarded by personnel officers, often disastrously.

In the production of psychiatric disabilities the intensity of combat is the main factor, and the infantry riflemen, who suffer the heaviest battle injuries, have also

the most combat exhaustion. There is a fairly consistent over-all proportion—for five men wounded one is killed and one disabled by combat exhaustion. An appreciable portion of those killed in action lost their lives because they lost their heads. Individual replacements inadequately integrated in their units, were subject to special psychiatric risks. Fatigue is a very important contributory cause of reduced capacity to withstand disruptive influences, but not an adequate cause in itself of the typical psychiatric disability of combat. Pre-existing mild neurosis did not appear to be of crucial importance in the primary occurrence of "combat exhaustion," but was influential in shaping the neurotic pattern in its clinical evolution when prompt "recovery" did not occur.

In considering the emotional play of forces in the combat soldier, many writers have given too exclusive attention to fear. Combat also strongly stimulates hostility, not only toward the enemy, but toward the more immediately present—or absent—officer or comrade, particularly if occasion for distrust arises, and such feelings of distrust, resentment or hostility were emotionally very disruptive, to the group and to the individual. The maintenance of a steady pattern of close in-group confidence and support is a crucial factor in preventing or postponing the psychiatric disabilities of combat.

DISCUSSION

Dr. Perrin H. Long: I do not want to discuss every paper on the program but I would like to discuss one or two things in Dr. Whitehorn's paper. I sat and shuddered in my seat when Dr. Whitehorn began discussing the term "Exhaustion" because I was responsible for it. It came about this way: As all learn, when they go into the armed forces, you do what you are told to do, and often not what you expected to do. One of my duties for the first six months in North Africa was to be the neuropsychiatric consultant. Three weeks after I arrived in North Africa, at the end of January, 1943 we had a considerable number of severe neuropsychiatric American casualties, primarily hysterical in type entering the British Hospitals east of Oran. There were no American hospitals in that area despite the fact that the whole 12th Air Force and a considerable number of other troops were in Tunisia.

I was sent to Tunisia early in February and arrived just in time to go through the whole Kasserine Pass episode. At that time, despite all injunctions, medical officers were sending all neuropsychiatric casualties back labelled as "shell-shock"; and one of the favorite treatments was the administration of morphine. After surveying the situation, I wrote a directive on the treatment of neuropsychiatric casualties for the North African Theater of Operations. At that time it seemed definite that one should eliminate the use of the term "shell-shock" by order, so by order of General Fredenhall, it was directed that none of these cases were to be labelled "shell-shock" at the Battalion Aid Station but were to be called "Anxiety States." Well, in a month I returned to the combat area and went around and talked to patients coming in to the hospital. The American soldier is a very smart fellow who reads his emergency medical tags and quickly gets on to what is written

on them. He was not being fooled at all. When we asked him what was the matter, he said "shell-shock." This was bad because the one thing we wanted to eliminate was the term "shell-shock," so just before the opening of the Northern Tunisian battle, I called a conference of II corps psychiatrists. By that time I not only had then Captain Hanson and Major Tureen up forward treating the neuropsychiatric casualties but also two 400-bed evacs whose Tables of Organization called for psychiatrists, and they had good psychiatrists. At the conference I proposed that something must be done about the term Anxiety State—because the boys were wise to it and still said they had "shell-shock." We discussed the matter and came to the conclusion that the best thing was to call the condition "Exhaustion"; and by order of General Bradley, every neuropsychiatric case in the forward areas was labelled "Exhaustion" on his E.M.T. We selected this term for the following reason.

I do not know what it was like in the E.T.O., and I am not going to compare the unfavorable aspects of one theatre unfavorably with those of another theatre; but I never saw a time when the Infantry in the North African theatre of operations was not terribly tired, except in the winter of 1944–45 when the war was stymied by the snow. These boys were terribly tired; you have no idea how tired they were. I have some pictures of men coming into a receiving tent, and some of these pictures are frightful. I am going to have them framed, together with some pictures of triumphal parades, not made by soldiers, but by generals, just for comparison. We thought that it would be good to divert their minds by saying: "You are just tired out, son; you are exhausted"; and on that basis, and that basis alone, the diagnosis, "Exhaustion", was selected for the forward areas. There neuropsychiatric casualties were differentiated initially in the Evacuation Hospital—this was before combat psychiatrists were in each division. Afterwards these patients were differentiated by the divisional psychiatrists in what we called the Divisional Rehabilitation Center which was placed at some distance from the Clearing Station. This was the origin of the term "Exhaustion" and from the Sicilian campaign on but two or three occasions—and I talked with thousands of psychiatric casualties—did I ever hear a man speak of "shell-shock."

Another thing I want to take exception to is about Dr. Grinker's narcosynthesis. Practically every patient in his group was one of Kenton's or Hanson's and narcosynthesis which was worked out by Hanson and others in the ground troops was used less and less after the first day it was put into use because the individuals who were practicing psychiatry in the forward area were promptly instructed by Captain Hanson in its use; and by and large, it came to be less and less used. We rarely used barbituates after our initial experience to give a patient rest unless it was clearly shown when he got to the rehalilitation center, or if he had to go back further, that he could not get rest without them. We had very little trouble with the rear echelon psychiatrists criticizing the practices of the forward echelon psychiatrists because we made it a principle in our theatre to rotate doctors forward and backward, so that all got an idea of what forward duty was like.

Finally, one of the great difficulties which I encounted—while exercising general

supervision in neuropsychiatry for 27 more months—was to keep the psychiatrists from producing in the command a state of morbid resentment. This was finally overcome in January, 1944; but one of the great difficulties in the problem of neuropsychiatry in the Army is that the commanding officer rules your life (if he tells you to do something, you do it). The commanding officers had to be convinced that neuropsychiatric casualties were not damned cowards or malingerers and that there was a reason why the psychiatrists' advice should be followed. Our commanding officers in the last 18 months of the life the Theatre had such confidence in their divisional and unit psychiatrists that they rarely made a move in respect to possible neuropsychiatric patients until they had the advice of their psychiatrist—no man could be courtmartialled before a general court. This shows that you can work out all these difficulties if you instruct your commanding officer properly. That is the important thing. As a matter of fact, you can do anything in medicine in the Army if you get the confidence of your commanding officer; and for that reason, after the command became educated—and it took about a year to do it—then they took the word of the psychiatrists and we had very little trouble with command thereafter.

Dr. Howard: Have you anything to add, Dr. Whitehorn?

Dr. Whitehorn: Only a word of appreciation for what Perrin Long brings to the discussion from his own experience, and appreciation, too, for the comment which was made with regard to the tendency to use less and less mechanical aids. I think this is in accordance with the last remark he made that as psychiatrists gain respectability and faith in their own work, sometimes through bitter experience, they have to rely less and less on accessory aids such as barbiturates.

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